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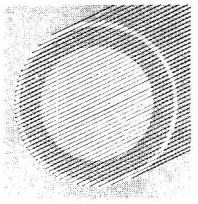

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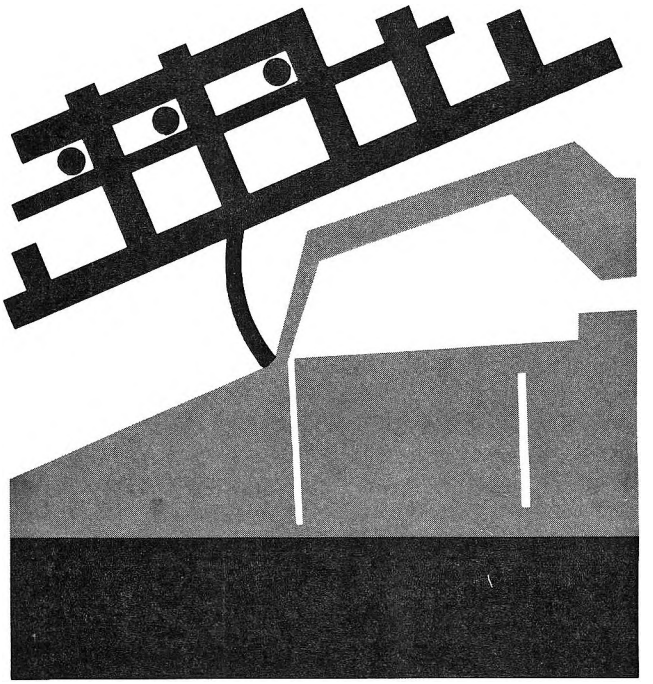

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Photochemical Cycloaddition of Cyclohexenone and Cyclopentenone to Conjugated Dienes[1a]

Thomas S. Cantrell

Departments of Chemistry, Rice University, Houston, Texas 77001, and The American University, Washington, D. C. 20016[1b]

Received August 27, 1973

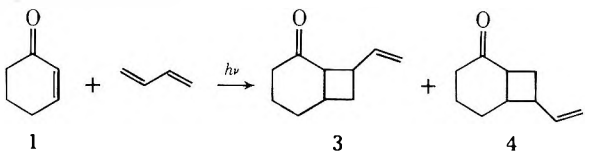
Cyclohexenone (1) and cyclopentenone (2) have been found to undergo [2 + 2] photochemical cycloaddition to conjugated dienes with moderate efficiency when the diene concentration is high, accounting for the erratic results sometimes obtained when certain 1,3-dienes are used as triplet quenchers for such enones. The products are mixtures of cyclobutanes resulting from [2 + 2] cycloaddition; in the addition of 1 and 2 to cyclopentadiene, the ratio of head-to-head to head-to-tail adducts was ~3:2. In the case of furan, a [4 + 2] cycloadduct was produced, as well as the usual [2 + 2] adducts. The experimental data are consistent with a mechanism involving attack of enone triplets on ground-state diene molecules.

The photochemical annelation of cyclic enones with unactivated olefins, developed only within the past decade,[2] has been the subject of recent intense interest with regard to its scope and mechanism. It is generally agreed that the reactive enone excited state is a triplet,[2b,3] that the annelation is nonconcerted, a radical- or diradical-like intermediate being involved, possibly preceded by complex formation between enone excited state and ground-state olefin.[3d,e,4] The reaction is usually limited to five- and six-membered cyclic enones, but these may bear certain substituents.[4] Such enones have been successfully added to olefins possessing a wide variety of either saturated or unsaturated substituents. It has been generally believed, even though no experimental observations appear to have been published, that enones add to conjugated dienes either not at all, or at best very inefficiently.[5] This seems reasonable, since energy transfer from the enone triplet excited states (E_T = 66–72 kcal) to a 1,3-diene (E_T = 53–60 kcal) should be exothermic by 6–20 kcal and therefore a rapid diffusion-controlled process, resulting in quenching of the enone triplet and production of diene triplets. Indeed, a powerful tool in mechanistic photochemistry, especially that of enones and dienones, has been the use of dienes such as 1,3-pentadiene and 1,3-cyclohexadiene as quantitative quenchers of triplet states of $E_T > 60$ kcal.[6]

Apparent exceptions have appeared. Schenck reported several years ago the benzophenone-sensitized addition of maleic anhydride ($E_T \cong 72$ kcal[7]) and dimethylmaleic anhydride to various dienes and trienes to give mixtures of [2 + 2] and [4 + 2] adducts.[8] Irradiation of duroquinone in the presence of dienes leads to both [2 + 2] and [4 + 2] adducts, as well as their products of further transformation;[9] however, transfer of triplet energy to the dienes should be inefficient here, since the quinone probably has $E_T \leq 50$ kcal. Also pertinent is the observation that saturated aldehydes and ketones undergo photoaddition to dienes to give vinyl oxetanes.[10] However, the evidence available implicates the intermediacy of carbonyl compound excited *singlet* states. On the other hand, Barltrop and Carless have very recently reported the isolation of photoadducts (oxetanes) from benzophenone and several 1,3-dienes, including 1,3-butadiene.[11] The oxetanes were formed inefficiently at the relatively low diene concentrations used (Φ = 0.0003 in 0.3–0.5 *M* diene) but were shown to arise from addition of ketone triplets to ground-state diene molecules. Finally, eucarvone (a 2,4-cycloheptadienone) has been reported to form [2 + 2] photoadducts with 1,3-dienes *via* triplet states.[12]

Results

We report here our observations that 2-cyclohexenone (1) and 2-cyclopentenone (2) do in fact undergo photochemical cycloaddition to several 1,3-dienes, usually in the [2 + 2] manner, and in the case of enone 1, with surprisingly high efficiency. By use of a large excess of the diene (≥10-mol excess) it is possible to obtain on a preparative scale good yields of most of the adduct mixtures under conditions of high conversion. For example, irradiation of 0.05 mol of 1 in the presence of a 20-fold excess of 1,3-butadiene gave an isolated yield of 72% of the adduct mixture of gross structures 3 and 4. In Table I are listed yields of adducts from irradiation of 1 and 2 with several representative dienes; these reactions were all run to essentially complete consumption of enone. There is usually observed concomitant formation of the diene dimers resulting from energy transfer from enone triplets to diene.[5] In those cases where this is a fairly efficient process, such as with 1 and 1,3-cyclohexadiene, there is a rapid early buildup of diene dimer and most of the enone is consumed by cycloaddition to the diene dimers.



1 3 4

five isomers

The adduct mixtures from all dienes except furan and cyclopentadiene were shown in each case to contain only

Table I

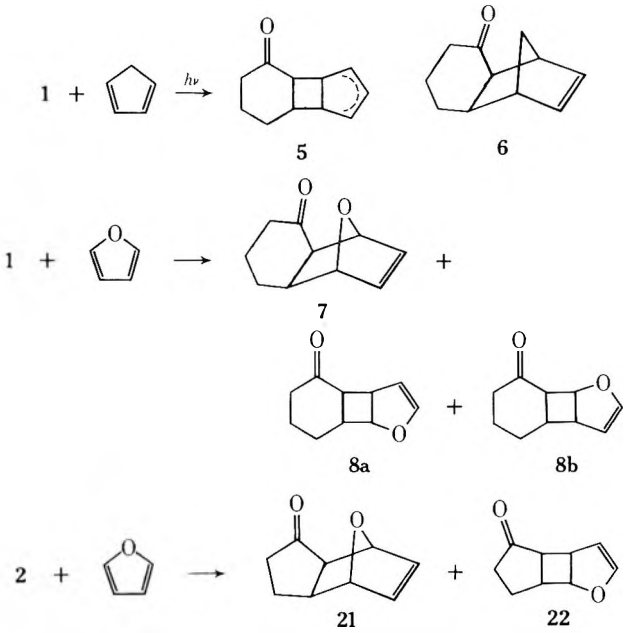
Registry no.	Diene	Yield of adducts, %[a]	Relative efficiency[b]	Number of adducts	Ratio
	Photoadditions of **1**[c]				
110-83-8	Cyclohexene		1.00	≥3	
106-99-0	1,3-Butadiene	72	0.65	5	24:38:17:16:5
542-92-7	1,3-Cyclopentadiene	47	0.41	4	48:16:21:15
592-57-4	1,3-Cyclohexadiene	16	~0.3–0.35	≥3	60:31:9
544-25-2	1,3,5-Cycloheptatriene	30	0.04	2	25:75
1700-10-3	1,3-Cyclooctadiene	78	0.58	3	13:70:17
27140-13-2	Spiro[2,4-hepta-2,5-diene]	55	0.5	3	
110-00-9	Furan	63	0.6	3	45:32:23
592-46-1	2,4-Hexadiene	40		≥4	
111-78-4	1,5-Cyclooctadiene	66	0.7	2	29:71
	Photoadditions of **2**[c]				
	1,3-Butadiene	32	0.10	3	
	Cyclopentadiene	27	0.14	2	37:63
	1,3-Cyclooctadiene	56	0.38	3	15:62:23
	Furan	47	~0.5	2	80:20

[a] Satisfactory elemental analyses and mass spectral molecular weight data were obtained on all adduct mixtures, and on individual compounds when the mixtures were resolvable. [b] Efficiency of addition to cyclohexene as standard; to obtain quantum yields for additions to dienes, multiply efficiencies by cyclohexene quantum yield (Φ = 0.45) under identical conditions; compare ref 3e. [c] Standard conditions: [enone] = 0.25 *M*; [diene] = 5.0 *M*. Runs were carried to ≤8% completion.

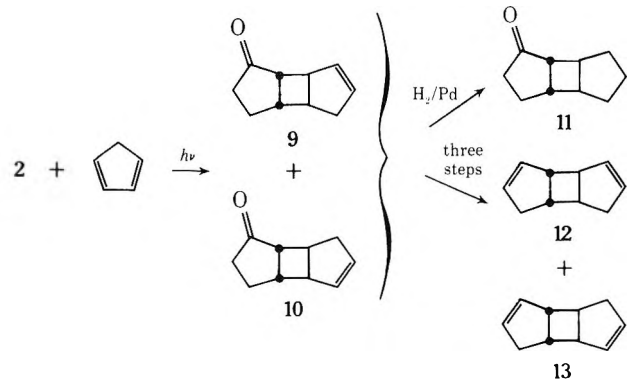
compounds resulting from [2 + 2] cycloaddition processes by the simple procedure of hydrogenation of the adducts and comparison of the resulting saturated ketones with those obtained by addition of **1** and **2** to the corresponding monoolefins. In some cases the individual components were isolated before hydrogenation, whereas in others the identification was simpler after hydrogenation, since the number of isomers was thus reduced by a factor of approximately 2. The composition of all product mixtures was checked at varying stages of completion and was found to be unchanged throughout the course of the reactions.

It would be anticipated that 1,4-addition would be most favorable in the case of a planar, cisoid 1,3-diene, such as cyclopentadiene or furan. In fact, **2** adds to cyclopentadiene entirely in the [2 + 2] fashion (*vide infra*) and **1** adds [2 + 2] to the extent of at least 85%. In the mixture from irradiation of **1** and cyclopentadiene, two of the four products were converted on hydrogenation to the known[3a] cis adduct of **1** and cyclopentene, and a third was reducible to the corresponding trans adduct. The fourth component of the product mixture, present to the extent of ~15% and not obtained entirely pure, exhibited nmr data [*inter alia*, signals at τ 3.9 (2 H, m) and for bridge methylene at 8.6 (2 H, m)], which are consistent with its formulation as a norbornene derivative (**6**). This material was not identical with the thermal [4 + 2] adduct of **1** and cyclopentadiene, prepared in low yield by heating the reactant at 170°. However, the thermal adduct is probably the isomer with the cyclohexanone ring fused endo,endo to the norbornene frame, whereas the photoadduct probably arises *via* a radical route (*vide infra*) not governed by orbital symmetry considerations and could have a different stereochemistry. Finally, if the adduct is the result of thermal addition of cyclopentadiene to a strained, photochemically produced trans enone, it should be one of the two trans-fused exo,endo isomers.[13]

Irradiation of **1** or **2** in furan resulted in both [2 + 2] and [4 + 2] addition. The stereochemistry of the [4 + 2] adducts, *e.g.*, **7**, is a matter of some interest since a trans ring fusion would imply the intermediacy of a strained ground-state trans enone *via* thermal [4 + 2] addition. However, the [4 + 2] adducts from **1** and **2** and furan proved to be thermally unstable and on attempted gas chromatographic purification underwent retro Diels–Alder reaction, reverting to **1** and **2**, respectively, and furan. The presence of **7** in the product mixture from **1** and furan was clear from the spectral properties of the mixture, the nmr signals for **7** at τ 3.7 (2 H, A part of AA′XX′), 5.1 and 5.4 (1 H each, broad singlets, -CHO-), and 6.5 (2 H, m, $-CH_2C{=}O$) being clearly separated from those attributable to **8a** at τ 3.6 (1 H, 2 d, J = 7.4, J' = 4.2 Hz, -OCH-) and 6.7 (2 H, m, $-CH_2C{=}O$) and to **8b**. The major [2 + 2] adduct, **8a**, obtained pure by gc, was identified by comparison of the product of its hydrogenation over palladium on charcoal with the major photoadduct from **1** and 2,3-dihydrofuran. Similarly, reduction of the major [2 + 2] adduct from **2** and furan gave a compound identical with the adduct of **2** and 2,3-dihydrofuran.



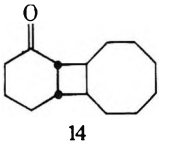
The addition of **2** to cyclopentadiene gave two products, **9** and **10**, in a 63:37 ratio. That these were [2 + 2] adducts differing only in the position of the double bond was shown by their conversion upon catalytic hydrogenation to the same saturated tricyclic ketone, **11**, identical with the adduct of **2** and cyclopentene, whose structure has been established as being the anti [2 + 2] product.[14]



The orientation of the adducts from **2** and cyclopentadiene, and also from **1** and 1,3-cyclohexadiene, was established by a combination of chemical degradation and synthesis. The adduct mixtures were converted to diolefins by a three-step sequence of (1) reduction with lithium aluminum hydride, (2) conversion to the corresponding secondary tosylates, and (3) elimination with *tert*-butoxide. The individual diolefins **12** and **13** were separated by gc and compared with authentic samples prepared by similar sequences from the photodimers of **1** and **2** whose structures have been rigorously proved.[15] In this way it was shown that the ratio of "head-to-head" to "head-to-tail" adducts from **2** and cyclopentadiene (**9** and **10**) was 63:37. Application of this method to the adduct mixture from **1** and 1,3-cyclohexadiene resulted in the isolation of the two major diolefins from the mixture, which were found to be identical with samples produced by degradation of the two *major* photodimers of **1**.[15b] The two major adducts from **1** and 1,3-cyclohexadiene were formed in a head-to-head:head-to-tail ratio of 69:31.

The predominance of head-to-head adducts is at first somewhat surprising, since the π-complex rule of orientations in photochemical cycloadditions would predict that in the more favored complex the more electron-rich terminal carbon of the diene should lie nearest C-2 of the enone, giving rise to head-to-tail adducts. The orientational selectivities observed here are not large in either case, and predictive rules appear irrelevant. However, the concept of the stability of the presumed biradical intermediate may have mechanistic implications here, if not predictive power. Since initial bond formation to the diene almost certainly takes place at one of the terminal diene carbons, it might appear that initial bonding to the enone occurs to an appreciable extent at both C-2 and C-3, with that at C-3 predominating. The only experimental results yet available having a bearing on the site of initial bonding to enone in photocycloadditions indicate that in the case studied (**2** to the symmetrical substrate 1,2-dichloroethylene) bonding occurs initially entirely at C-3.[16] The quantitative validity of this result has been questioned, however.[2b] Further, the initial bonding step may be reversible, in which case no conclusions can be drawn from the orientations observed here.

The product yields and relative quantum yields in the photochemical cycloaddition of **1** and **2** to the other dienes studied are given in Table I and do not require further comment. The facile addition of **1** to 1,3-cyclooctadiene was unsurprising and was expected even before the fact, since this twisted diene probably has a triplet energy of 70–72 kcal[17] and energy transfer from enone triplets should be endothermic and thus not favored. The addition of **1** and **2** to 1,5-cyclooctadiene was studied in order to search for products resulting from 1,5-cyclization of the presumed diradical intermediate. 1,5-Cyclooctadiene undergoes bridging during the addition of many, but not all, radicals to yield 2,6-disubstituted bicyclo[3.3.0]octanes.[18] In fact, the two adducts, formed in a 42:58 ratio by photochemical addition of **1** to 1,5-cyclooctadiene, were converted upon hydrogenation to two saturated tricyclic ketones. These proved to be identical with the two major adducts from **1** and cyclooctene itself, and must therefore by the cis- and trans-fused isomers of structure **14**. Base-



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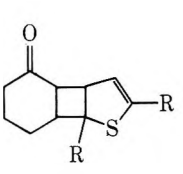
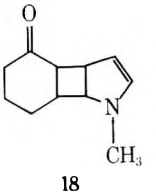
catalyzed equilibration experiments indicated the major (58%) isomer to be that possessing the cis 6:4 ring fusion.

Finally, we studied the behavior of excited **1** toward thiophene, 2,5-dimethylthiophene, and *N*-methylpyrrole, and of carbostyril [(1*H*)-2-quinolone, **15**] to furan. Irradiation of **1** in neat thiophene gave mainly dimers of **1**, but there could be isolated by repeated fractional distillation 8% of an adduct whose spectral data indicate it to be the result of [2 + 2] addition of **1** to thiophene. The two vinyl hydrogens in the adduct's nmr spectrum appear at τ 3.84 and 4.41. In the spectrum of 2,3-dihydrothiophene itself H_4 and H_5 appear at τ 4.52 and 3.94.[19a] In 2,5-dihydrothiophenes with almost identical alkyl substituents on C-2 and C-5, such as 7-thianorbornenes, the vinyl hydrogens have almost identical chemical shifts.[19b] 2,5-Dimethylthiophene has been reported to be considerably more reactive than thiophene itself toward benzophenone triplets.[20] This difference in reactivity extended to excited **1** and we were able to isolate 43% of a mixture of [2 + 2] adducts, **17**. The orientation of **16** and **17** was not experimentally



16, R = H
17, R = CH_3



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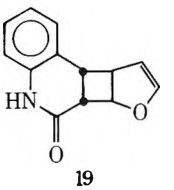

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determined, but was inferred by analogy with the orientation of **8** and **22**, established as described earlier (*vide supra*).

Irradiation of **1** in the presence of *N*-methylpyrrole gave a mixture of unstable adducts which underwent hydrolysis to give material whose ir and nmr spectra exhibited signals characteristic of aldehydic C–H bonds. This would appear to indicate the presence of an enamine function and, consequently, a [2 + 2] structure such as **18** for at least one of the adducts.

Irradiation of carbostyril in ethanol–furan mixtures gave the known carbostyril photodimer and a single adduct, **19**, mp 201–202°; hydrogenation of this adduct gave dihydro-**19**, mp 194–195°. Photochemical addition of carbostyril to 2,3-dihydrofuran gave an adduct, **20**, mp 174–175°, whose

20

orientation and stereochemistry were assigned as shown by analogy with the known photoproduct from carbostyril and ethyl vinyl ether.[21] Compound **20** was in every respect

Table II

Diene concn, M[a]	Ratio of diene dimers/adducts[b]
0.12	0.28
0.25	0.35
0.50	0.48
1.0	0.90
2.0	1.8
4.0	3.2

[a] Enone concentration in all runs was 0.10 M. [b] Runs were carried to 8% completion.

different from dihydro-**19**, eliminating from consideration the anti, head-to-tail structure for **19**. That **19** possesses the orientation shown (head-to-head) was deduced from examination of its 220-MHz nmr spectrum. Previous workers have reported that in the nmr spectra (220 MHz) of adducts from carbostyril and several olefins, the signal due to H-3 appeared in every case at higher field (0.15–0.87 ppm) than that due to H_4. Consequently, we assign the signals at τ 6.28 and 6.51 in the spectrum of **19** to H-4 and H-3, respectively. When the spectrum was scanned while simultaneously irradiating the signal at τ 4.85, attributable only to the proton α to the furan oxygen (H-2′ in the formula below), the H-3 multiplet collapsed from a doublet of multiplets to a single multiplet. This demonstration that H-2′ and H-3 are strongly coupled (J = 7.4 Hz) leads to the above orientational assignment. In the photochemical additions of carbostyril examined by Evanega and Fabiny in which more than one adduct was isolated, analysis and decoupling experiments invariably indicated the major adduct to have the head-to-tail anti stereochemistry. One may conclude from this that photoexcited carbostyril adds initially at C-3, since excited triplet benzophenone adds to furan to give solely the product from reaction of the carbonyl oxygen with C-2 of furan.[22]

Finally, the rates of formation of both adducts and diene dimers were measured for the cyclohexenone–butadiene system at several diene concentrations. The data (Table II) show that the rate of adduct formation increases with increasing diene concentration, and that the rate of diene dimer production shows an even greater dependence on diene concentration. Interestingly, the ratio of these two rates showed an approximately linear dependence on diene concentration (Figure 1). Unfortunately, we have no quantitative explanation for this behavior. Since at least one step in the enone photoannelation process (and, presumably, in the dimer-forming process) is thought to be reversible,[23] the kinetics of these systems is quite complex. The photoannelation of enones with monoolefins is generally regarded as originating *via* excited triplet ketone;[2] it seems most likely that the presently observed adducts with dienes arise *via* a similar intermediate. However, a satisfactory analysis which accounts for both (a) the success of the adduct-forming process in competition with energy transfer to ground-state diene, and (b) why cyclopentenone adds more slowly to dienes than does cyclohexenone and yet gives diene dimers faster than 1 awaits the availability of additional quantitative data.

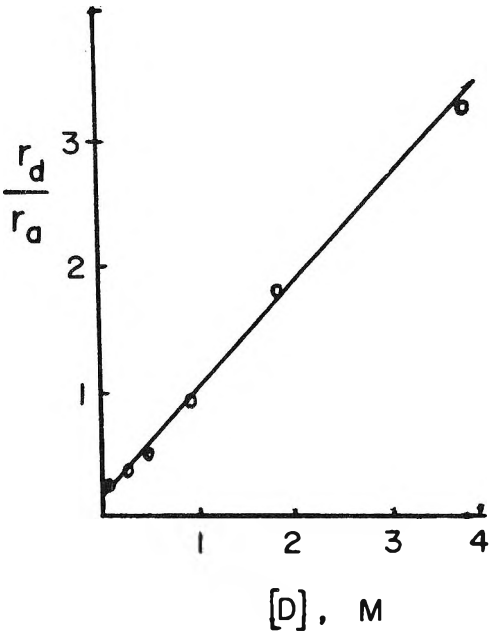


Figure 1. Plot of data in Table II.

Experimental Section

General. All dienes were the purest grade commercially available and were freshly distilled before use in each case. The enones employed, 2-cyclopentenone and 2-cyclohexenone, were obtained from the Aldrich Chemical Co. and were redistilled under reduced pressure and stored at −20°. Gas chromatography indicated each to be >98% pure. Analytical gas chromatography was performed on the following columns: column A, 5 ft × 0.25 in., 5% SE-30 silicone rubber on Chromosorb P; column B, 5 ft × 0.25 in., 5% Carbowax 20M on Chromosorb P; column C, 10 ft × 0.25 in., 10% OF-1 fluorosilicone rubber on Chromosorb W; column D, 10 ft × 0.125 in., 5% Carbowax 20M on Chromosorb W; and column E, 12 ft × 0.125 in., 5% Apiezon L on Chromosorb P. Preparative gas chromatographic separations were accomplished on columns B and C, mentioned above, or on column F, 6 ft × 0.375 in., 20% SE-30 on Chromosorb P, and column G, 10 ft × 0.375 in., 20% Carbowax 20M on Chromosorb P. The instrument was a Varian Aerograph Model 202-1B, equipped with a thermal conductivity detector. Infrared spectra were obtained on a Beckman IR-8 instrument, while nuclear magnetic resonance spectra were determined on a Varian A56-60A instrument operating at 47°. Elemental analyses were performed by the Elek Co., Torrance, Calif.

General Procedure for Enone–Diene Photoadditions. The apparatus consisted of a cylindrical Pyrex vessel which surrounded a Pyrex immersion well and was fitted by means of side arms to a condenser and a small serum bottle cap. Ice water at 5–8° was circulated through the annular space of the Pyrex well and also through an external bath in which the apparatus was immersed. In irradiations involving 1,3-butadiene or cyclopentadiene, coolant at −25° was circulated through the immersion well in order to prevent loss of 1,3-butadiene by evaporation and to retard thermal dimerization of cyclopentadiene. Solutions of 0.02 mol of enone, 0.2–0.4 mol of diene, and sufficient benzene to give a total volume of *ca.* 100 ml were prepared and flushed with prepurified nitrogen for 1 hr. The solutions were then irradiated with a Hanovia 450-W medium-pressure mercury arc, under a slight positive pressure of nitrogen. The progress of the reactions was monitored by gas chromatographic or infrared spectral means. After evaporation of the excess diene, the residue was fractionally distilled to separate diene dimers and the adducts. In many cases (see below) individual components of the adduct mixtures could be isolated by preparative gc. Yields of adduct mixtures are given in Table I.

Cyclohexenone and 1,3-Butadiene. Irradiation of a solution of 2-cyclohexenone (**1**, 4.0 g, 0.040 mol) and freshly distilled 1,3-butadiene (56 g, 1.0 mol) made up to 200 ml in benzene for 4 hr resulted in the isolation of 5.4 g of butadiene dimers, bp 40–44° (16 mm), and the recovery of 0.6 g of unchanged cyclohexenone (**1**). The mixture of [2 + 2] cycloadducts, **3** and **4**, was obtained as a colorless, sweet-smelling oil: bp 50–52° (0.3 mm) (3.7 g, 72%); ir (film) 1722, 1709 cm^{-1} (C=O); nmr ($CDCl_3$) τ 3.8–4.5 (1 H, X parts of ABX's); 4.7–5.3 (2 H, AB portions of ABX's), and 7.0–8.7 (11 H, m); mass spectrum m/e (rel intensity) 150 (parent, 87), 121 (62), 93 (56), and 78 (100). *Anal.* Calcd for $C_{10}H_{14}O$: C, 80.04; H, 9.30. Found: C, 79.82; H, 9.17.

Analysis on column C showed five partially resolved peaks with areas in the ratio (in order of increasing retention time) 21:17:26:30:6.

A solution of the above-described cyclohexenone–butadiene adduct mixture (1.5 g, 0.010 mol) in ethyl acetate was shaken with 10% palladium on charcoal (0.10 g) under 2 atm hydrogen pressure until absorption had ceased (20 min). Filtration of the catalyst, evaporation of the solvent, and distillation gave the dihydro adduct mixture, bp 49–52° (0.3 mm) (1.3 g, 88%). A solution of

this mixture in ether (50 ml) was stirred with neutral, activity I Woelm alumina for 44 hr. Filtration of the mixture and evaporation of the ether gave a colorless oil which showed three peaks on column D in the ratio 24:55:21.

Irradiation of a solution of 2-cyclohexenone (1, 1.0 g, 0.01 mol) and 1-butene (20 g, 0.50 mol) in benzene (90 ml) for 2 hr, followed by distillation of the solvent and excess 1-butene, gave an adduct mixture, bp 52–54° (0.5 mm), ir (film) 1710 cm^{-1}, *m/e* 152 (parent), which showed three peaks on columns D and E of the same retention times as those mentioned above, in the ratio 35:48:17.

Cyclohexenone and Cyclopentadiene. A solution of 2-cyclohexenone (4.0 g, 0.040 mol) and freshly distilled cyclopentadiene (66 g, 1.0 mol), made up in benzene to 220 ml, was irradiated at −20° for 3 hr. The solvent and excess cyclopentadiene were removed by evaporation under reduced pressure, maintaining the reaction mixture at 0° or below. Fractional distillation gave the following fractions: (A) cyclopentadiene dimers, bp 32–36° (5 mm), 6.1 g; (B) a mixture of adducts, bp 72–74° (0.3 mm), 4.7 g (0.026 mol. 66%); and (C) a fraction. bp 150–160° (0.2 mm), 0.9 g, which appeared to be composed of adducts of 1 with cyclopentadiene dimers. The 1:1 adduct mixture, fraction B (5 and 6), showed the following spectral data: ir (film) 1710 (s) and 1601 cm^{-1} (w); nmr (CCl_4) τ 3.9–4.4 (2 H, m), 6.7 (1 H, m), 6.9 (1 H, m), and 7.4–8.6 (10 H, m, $-CH_2$'s); mass spectrum *m/e* (rel intensity) 162 (parent, 24), 106 (27), 97 (100), and 91 (63). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.51; H, 9.63. Found: C, 81.20; H, 9.77.

This material was shown by analysis on column D at 200° to be a mixture of four isomers of the following relative areas: 48:16:21:15.

A sample of the mixture in ethyl acetate (50 ml) was shaken under 15 psig hydrogen pressure for 2 hr; filtration and evaporation gave a colorless oil which showed two major and one minor components on columns B and D, of retention times (column B, 190°) 10.5 (63%), 12.1 (21%), and 12.5 min (15%). Photoaddition of 1 to cyclopentene as described by Corey, *et al.*,[3a] gave a mixture of the two major components in a 73:27 ratio (the cis- and trans-fused compounds, respectively) in our hands. The identity of the two saturated tricyclic ketones from the two sources was shown by comparison of the infrared spectra of collected samples and by identity of retention times on columns A, B, and D. The spectral features of the third component were given earlier, in the text.

Cyclohexenone and 1,3-Cyclohexadiene. A solution of 1 (5.0 g, 0.050 mol) and 1,3-cyclohexadiene (30 g, 0.38 mol) in sufficient benzene to make 220 ml of solution was irradiated under the standard conditions for 4.5 hr. Distillation gave first cyclohexadiene dimers (21 g), bp 45–53° (0.4 mm), and then a fraction showing carbonyl absorption (3.8 g), bp 60–120° (0.3 mm). Redistillation of the second fraction through a wire-spiral column gave a mixture of 1:1 adducts: bp 92–94° (0.3 mm) (1.6 g, 0.09 mol, 18%); ir (film) 1702 cm^{-1}; nmr (CCl_4) τ 4.17 (2 H, s, br) and 7.0–8.9 (14 H, m); mass spectrum *m/e* 178 (parent). *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.84; H, 9.08. Found: C, 82.29, H, 9.14. The mixture showed three poorly resolved peaks on columns C and D, of approximate ratio 40:50:10.

Conversion of the 1-Cyclohexadiene Adducts to Tricyclo[6.4.0.0]dodecadienes. A solution of the mixture of adducts from 1 and 1,3-cyclohexadiene (1.5 g) in methanol (30 ml) was added slowly to sodium borohydride (2.0 g) in 90% aqueous methanol at 30–40°. The solution was stirred for an additional 4 hr, after which the solvent was evaporated, water was added, and the reaction mixture was extracted four times with ether. Drying and evaporation of the ether extracts gave the mixture of alcohols (1.3 g), ν_{max} 3450 cm^{-1} (br).

The crude mixture of alcohols thus obtained (1.3 g) was converted directly to the corresponding tosylates by treatment with *p*-toluenesulfonyl chloride (2.5 g) in dry ether (50 ml) at 0–5° for 30 hr. Treatment with ice and water and extraction with ether (4 × 50 ml), followed by washing of the extracts with dilute hydrochloric acid solution, dilute sodium bicarbonate, and saturated brine, drying, and evaporation of the ether gave the tosylate mixture as a colorless oil (2.0 g). This material was dissolved in dry dimethyl sulfoxide (10 ml) and treated at 25–35° with a solution of freshly sublimed potassium *tert*-butoxide (0.90 g) in dimethyl sulfoxide (15 ml). After the solution has stood at room temperature for 2 hr, it was poured onto an ice-water slurry and the resulting mixture was extracted three times with pentane. The combined extracts were tricyclic dienes as a colorless oil, bp 46–49° (0.4 mm) (0.62 g, 41%). This material was sufficiently well resolved on a 10 ft × 0.25 in. Apiezon L column to allow collection of the two major components, which amounted to 56 and 34% of the total. These were found to be identical with the independently prepared samples of tricyclo[6.4.0.$0^{2,7}$]dodeca-3,11-diene and the 3,9-diene, respectively (*vide infra*).

Synthesis of Authentic Tricyclododecadienes. A mixture of the photodimers of 1 was prepared according to the procedure of Hammond, *et al.*, which was stated to give the head-to-head anti, the head-to-tail anti, and two other isomers in a ratio of 25:60:15. Degradation of this mixture was performed in the same way as was the conversion of the individual cyclopentenone photodimers to the corresponding diolefins (*vide infra*). Thus, a solution of 5.0 g of the dimer mixture in ether (100 ml) was added to excess lithium aluminum hydride, and the solution was refluxed for 2 hr and worked up in the fashion described below. Treatment of the crude oily mixture of diols with tosyl chloride (12 g) in dry pyridine (50 ml) at 0–5° for 4 hr, dilution with ice water, and repeated extraction with ether gave a thick oil. To this oil (6.5 g) in *tert*-butyl alcohol (30 ml) was added freshly sublimed potassium *tert*-butoxide (4.0 g) in portions, with cooling to keep the temperature below 25°. The mixture was shaken at 25° for 0.5 hr and then poured into ice water. Extraction with pentane, washing several times with water, and evaporation of the solvent gave a colorless oil, which was distilled to give a diolefin mixture, bp 45–49° (0.4 mm) (0.9 g). The two major components of the mixture (62 and 27% of the total) were found to be identical with the two major components of the mixture obtained by degradation of cyclohexenone–cyclohexadiene adduct mixture.

Photoaddition of 2-Cyclohexenone to 1,3,5-Cycloheptatriene. A solution of 1 (2.0 g, 0.020 mol) and redistilled cycloheptatriene (46 g, 0.50 mol) in sufficient benzene to make 120 ml of solution was irradiated for 30 hr under the standard conditions. There was obtained 2.6 g of a yellow oil, bp 70–80° (bath) (0.1 mm). Preparative gc on column F gave first a mixture of cycloheptatriene dimers (30% of total area, two peaks on column C, in the ratio 28:72): ir (film) 1657 cm^{-1} (m); nmr (CCl_4) τ 4.0–4.7 (8 H, m) and 6.8–8.4 (8 H, m); mass spectrum *m/e* (rel intensity) 184 (parent, 48), 92 (100), and 91 (86). *Anal.* Calcd for $C_{14}H_{16}$: C, 91.34; H, 8.66. Found: C, 91.02; H, 8.31.

The third and fourth peaks (70% of area, 44% yield) were incompletely resolved, but were obviously adducts of 1 and cycloheptatriene: ir (film) 1703 cm^{-1}; nmr ($CDCl_3$) τ 4.1 (4 H, m) and 6.8–8.6 (12 H, br, m); mass spectrum *m/e* (rel intensity) 188 (parent, 46), 104 (51), 92 (96), 91 (100); uv (EtOH) 250 nm (ϵ 2300). *Anal.* Calcd for $C_{13}H_{16}O$: C, 82.13; H, 8.41. Found: C, 82.36; H, 8.19. Hydrogenation of this adduct mixture (0.50 g) over palladium on charcoal in ethyl acetate led to the uptake of 2 equiv of hydrogen and gave, after work-up, 0.44 g of a saturated tricyclic ketone mixture, ν_{max} 1704 cm^{-1}, which showed two peaks on column B at 180°. Their retention times were identical on columns A, B, and C, to those of the two components of the ketone mixture obtained in 61% yield on photochemical addition of 1 to cycloheptene. The ir spectra of the collected ketones were superimposable.

Photoaddition of 2-Cyclohexenone to 1,3-Cyclooctadiene. A solution of 1 (2.0 g, 0.020 mol) and 1,3-cyclooctadiene (43 g, 0.40 mol) in sufficient benzene to make 125 ml of solution was irradiated under the standard conditions for 2.5 hr. Evaporation of the excess diene under reduced pressure and short-path distillation of the residue gave the adduct mixture, bp 90–95° (bath) (0.2 mm) (2.35 g, 66%). This material was shown by analysis on column C at 190° to be composed of three isomers, in the ratio 13:70:17, of retention times 15.5, 17.2, and 18.3 min, respectively. The first and second components were collected from column G at 230°. The first peak, obtained as a colorless oil, showed ir (film) 1700 cm^{-1}; nmr (CCl_4) τ 4.3 (2 H, br) and 6.9–8.6 (18 H, br); mass spectrum *m/e* (rel intensity) 204 (parent), (41), 175 (33), 108 (29), 105 (40), and 79 (100). *Anal.* Calcd for $C_{14}H_{20}O$: C, 82.38; H, 9.80. Found: C, 82.57; H, 9.71.

The second major component was a solid and could be obtained pure by direct low-temperature crystallization of the mixture, as well as by gc. Recrystallization from 10% chloroform–hexane at 0° gave thick white prisms: mp 78.5–79.5°; ir (KBr) 1698 cm^{-1}; nmr ($CDCl_3$) τ 4.1–4.7 (2 H, m) and 6.9–8.5 (18 H, m, br); mass spectrum *m/e* (rel intensity) 204 (parent, 57), 175 (43), 147 (18), 133 (16), 119 (16), 108 (25), 105 (32), 91 (73) 79 (100), and 67 (54). *Anal.* Found: C, 82.25; H, 9.62.

A solution of the adduct mixture (0.50 g) in ethyl acetate (20 ml) was shaken for 1 hr over palladium on charcoal under 15 psig hydrogen pressure. The colorless oil obtained after filtration of the catalyst and evaporation of the solvent showed two peaks on columns C and D at 180° in the ratio 87:13. Collection of the peaks and infrared analysis showed them to be identical with the

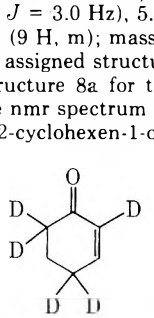
two major adducts from 1 and cyclooctene. Thus, all three adducts must result from [2 + 2] cycloaddition.

Photochemical Cycloaddition of 1 to 1,5-Cyclooctadiene. A solution of 1 (2.0 g, 0.020 mol) and freshly distilled 1,5-cyclooctadiene (32 g, 0.030 mol) in sufficient benzene to make 130 ml of solution was irradiated for 3 hr under the standard conditions. The usual work-up gave a colorless oil: bp 116–120° (0.1 mm) (2.9 g, 64%); ν_{max} 1700 cm^{-1}; nmr (CCl_4) τ 4.4 (2 H, m) and 7.4–8.7 (18 H, complex m); mass spectrum *m/e* (rel intensity) 206 (parent, 91), 178 (35), 163 (35), 97 (100), 91 (70), 79 (100), and 67 (66). *Anal.* Calcd for $C_{14}H_{20}O$: C, 82.38; H, 9.80. Found: C, 82.10; H, 9.59.

Hydrogenation of this ketone mixture (0.70 g) in ethyl acetate solution in the presence of 10% palladium on charcoal (50 mg) for 1 hr led to solvent, and distillation gave 0.62 g (90%) of a colorless oil which showed two peaks in the ratio 42:58 (column C at 190°) which were identical (ir, retention times) with the two saturated ketones obtained in a ratio of 87:13 from reduction of the 1-1,3-cyclooctadiene adducts. Photochemical addition of 1 to *cis*-cyclooctene (3 hr through Pyrex) gave 66% of a mixture of three saturated tricyclic ketones in the ratio 56:40:4. The first two of these were identical (ir, gc) with the two saturated ketones obtained from reduction of the adducts from 1,3- and 1,5-cyclooctadiene, thus showing that both adducts from the two dienes resulted from 1,2-addition.

Exposure of an ether solution of the adduct mixture from 1 and cyclooctene (200 mg in 20 ml) to sodium methoxide (40 mg) for 12 hr at 25° resulted in isomerization of the first and third components. After neutralization, pouring into water, and work-up, the recovered ketone mixture was found to contain the first and second components in the ratio 73:27. Apparently the second isomer possesses a trans 6–4 ring transfusion.

Photoaddition of 1 to Furan. A solution of 2-cyclohexenone (4.0 g, 0.040 mol) in furan (125 ml) was irradiated under the standard conditions for 3 hr. The residue remaining on evaporation of the excess furan was evaporatively distilled in a short-path apparatus to afford an adduct mixture as a faintly yellow oil, bp 70° (bath) (0.08 mm) (4.1 g, 63%). *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.19; H, 7.30. Found: C, 72.88; H, 7.35. The nmr spectrum of the mixture showed, in addition to signals due to **8a** and **8b** (*vide infra*), additional signals for **7** at τ 3.72 (2 H, A part of AA′XX′, vinyls), 5.13 (1 H, m, HCO), 5.40 (1 H, m, HCO), and 6.5 (1 H, m, CHC=O). From the respective area ratios, the mixture contained *ca.* 40% of 7. Adduct 7 underwent retro Diels–Alder cleavage on attempted glc separation. On column A at 180°, three peaks were present, of retention times 4.0, 13.7, and 14.5 min, of relative areas 40:35:25. The first of these was shown to be 1 by comparison of infrared spectra. The second peak was identified as the [2 + 2] adduct **8a**: nmr ($CDCl_3$) τ 3.61 (1 H, 2 d, J = 2.8, J' = 1.4 Hz, -C=CHO), 4.80 (1 H, apparent t, J = 2.8 Hz, -OCH=CHC), 5.01 (1 H, 2 d, J = 7.4, J' = 4.2 Hz, -OCH-), 6.7 (2 H, m, $-CH_2C$=O), and 7.2–8.6 (7 H, m); ir (film) 1706 (s, C=O), 1600 cm (s, -OC=C); mass spectrum *m/e* (rel intensity) 166 (parent, 15), 81 (17), 79 (13), 68 (100), and 55 (28). The third peak [ir (film) 1704 cm^{-1}; nmr ($CDCl_3$) τ 3.7 (1 H, m), 4.81 (1 H, apparent t, J = 3.0 Hz), 5.24 (1 H, 2 d, br, J = 8.4, J' = 4.5 Hz), and 6.7–8.2 (9 H, m); mass spectrum *m/e* (rel intensity) 166 (18), 68 (100)] is assigned structure **8b** on the basis of (a) the establishment of structure 8a for the major [2 + 2] adduct (*vide infra*), and (b) the nmr spectrum of deuterated adduct **22**. 2,4,4,6,6-Pentadeuterio-2-cyclohexen-1-one (**21**) was prepared by the usual



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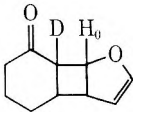

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base-catalyzed exchange with D_2O. Two cycles gave material whose nmr spectrum indicated was ~85% deuterated in the 2 position. Irradiation of **21** in the manner described above, distillation of the product, and collection of the minor peak (that of longer retention time) from column A gave a colorless oil, whose nmr spectrum showed a signal at τ 5.2 which had collapsed from the pair of doublets in the spectrum of **8b** to a single broad doublet ($J \cong 8$ Hz). This signal must be due to H_o and its appearance in the spectrum of the deuterated adduct demonstrates that H_o and the proton α to carbonyl are strongly coupled, and must be on adjacent carbon atoms, as in **22**.

A sample of the distilled adduct mixture (1.2 g) in ethyl acetate was shaken under 15 psig hydrogen pressure with 10% palladium on charcoal (50 mg). After 45 min, reduction was complete; the catalyst was then filtered and the solvent was evaporated. Analysis of the residue on column C at 180° showed three peaks at 8.5, 9.2, and 11.0 min, in the ratio of 16:44:40. The second peak was collected and found to be identical (ir, gc retention times on columns B and C) with the major product of addition to 1 to 2,3-dihydrofuran. The minor peaks were not further investigated.

Irradiation of 1 with 2,3-Dihydrofuran. A solution of 1 (2.0 g) and 2,3-dihydrofuran[24] (35 g) in benzene (80 ml) was irradiated under the standard conditions for 3 hr. Distillation of the excess olefin and evaporation of the benzene, followed by distillation of the residue, gave 2.3 g (64%) of a colorless oil, bp 74–80° (0.1 mm), ir 1706 cm^{-1}. Analysis on column C at 180° showed two peaks, of retention times 9.2 and 11.5 min, in the ratio 69:31. The major peak was identical with one of the components from the hydrogenation of the 1-furan product mixture (*vide supra*).

Photochemical Cycloaddition of Cyclopentenone (2) to Cyclopentadiene. A solution of **2** (4.1 g, 0.050 mol) and freshly distilled cyclopentadiene (60 g, 0.90 mol) in sufficient benzene to afford 220 ml of solution was irradiated in the usual fashion while being cooled externally with an ice–salt bath at −15°, and with chilled glycol–water (−20°) being circulated through the immersion well. After 3 hr of irradiation, the solvent and excess cyclopentadiene were evaporated under reduced pressure, care being taken to keep the solution below 5°. Fractional distillation under reduced pressure of the residue thus obtained afforded three fractions: (a) cyclopentadiene dimers, bp 30–32° (1 mm), 6.1 g; (b) an adduct mixture, bp 51–54° (0.3 mm), 2.3 g (37%); and (c) enone-dimer adducts, bp 115–130° (0.3 mm), 2.0 g (24%), in addition to a tarry residue. Redistillation through a 15-cm Vigreux column of fraction b from two such reactions gave the mixture of the adducts **9** and **10** as an almost colorless oil: bp 51–53° (0.3 mm); ir (film) 1730 cm^{-1}; nmr ($CDCl_3$) τ 3.8–4.6 (2 H, m), 6.9–8.7 (10 H, m); mass spectrum *m/e* (rel intensity) 148 (parent, 27), 106 (36), 83 (60), 82 (100), and 65 (48). *Anal.* Calcd for $C_{10}H_{12}O$. A solution of the above adduct mixture (2.1 g, 0.015 mol) in methanol (20 ml) was treated with excess sodium borohydride in methanol, with external cooling to keep the temperature below 30°. After being stirred for 2 hr further at room temperature, the reaction mixture was poured onto an ice–water slurry and extracted with ether. The ether extracts were washed exhaustively with water, dried ($MgSO_4$), and evaporated to yield the alcohol mixture (1.9 g). This material, without further purification, was treated in pyridine (10 ml) with *p*-toluenesulfonyl chloride (2.8 g) in pyridine at 0–4° and stirred at that temperature for 5 hr, then let stand overnight in the refrigerator. The reaction mixture was poured into ice-cold 10% hydrochloric acid and extracted with ether (3 × 15 ml), and the extracts were washed once with cold 10% HCl, twice with cold 5% sodium bicarbonate, and then with cold water, and dried. Evaporation of the ether gave the tosylate mixture as a viscous oil which was dissolved in dry dimethyl sulfoxide (25 ml) and treated at 20–25°, while being vigorously stirred, with freshly sublimed potassium *tert*-butoxide (2.2 g). After 1 hr, the dark brown reaction mixture was poured into water and extracted with pentane (3 × 15 ml). The pentane extracts were washed with water, dried, and evaporated to give a colorless oil, bp 35–39° (4 mm) (0.82 g), which was shown by analysis on column A to consist of two components in the ratio 38:62. These were collected from column D and were found to be identical with authentic samples of tricyclo[5.3.0.0]deca-3,9- and -3,11-diene, respectively (*vide infra*).

The head-to-head and head-to-tail dimers of cyclopentenone, mp 65 and 126°, respectively, were prepared as described by Eaton.[15a] A solution of the head-to-head dimer (3.0 g) was dissolved in tetrahydrofuran (200 ml) and added dropwise to 1.8 g of lithium aluminum hydride in refluxing 1:1 ether–tetrahydrofuran (100 ml). The reaction mixture was treated successively with water (1.8 ml), 10% sodium hydroxide (1.8 ml), and water (6 ml). After stirring for an additional 1 hr, the resulting white suspension was filtered and the solid was washed twice with tetrahydrofuran. The combined filtrates were evaporated to give the product diols as a white solid (2.8 g). Recrystallization gave the major isomer as white prisms, mp 188–189° (1.8 g). *Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.47; H, 9.53. Found: C, 71.65; H, 9.71.

The major diol (1.7 g) in dry pyridine (20 ml) was treated with *p*-toluenesulfonyl chloride (3.2 g) in pyridine (20 ml) at 0–5°, and stirred at that temperature for 6 hr. The reaction mixture was poured into ice water and extracted with ice-cold ether (4 × 15 ml) and the ether extracts were washed with cold 15% hydrochlo-

ric acid (4 × 30 ml), 5% sodium bicarbonate, and water. Drying and evaporation of the extracts gave the corresponding ditosylate as a white solid (2.9 g). A sample had mp 177–178° dec after recrystallization from tetrahydrofuran. Treatment of the ditosylate (2.5 g) in dry dimethyl sulfoxide (25 ml) with freshly sublimed potassium *tert*-butoxide (3.0 g) at 40° for 35 min gave, after pouring the reaction water, extraction with pentane, and work-up, diene **13**, tricyclo[5.3.0.0]deca-3,9-diene, as a clear liquid, bp 42–44° (4 mm) (0.65 g). This diene was identical with the *minor* diene obtained from degradation of the adduct mixture from **2** and cyclopentadiene, as shown by the identity of their ir spectra and gc retention times on columns A, B, and D.

Similarly, the head-to-head dimer of cyclopentenone was converted to the corresponding diolefin; no sharp-melting diols or ditosylates were obtained during the sequence. The diene thus obtained was identical in all respects with the *major* product from degradation of the adduct mixture from **2** and cyclopentadiene.

Photochemical Cycloaddition of 2-Cyclopentenone to 1,3-Butadiene, 1,3-Cyclooctadiene, and Furan. Irradiation of **2** (3.5 g) and 1,3-butadiene (50 g) for 5 hr gave, in addition to 1.5 g of recovered **2**, an adduct mixture (1.2 g, 37% based on unrecovered enone): bp 41–44° (0.3 mm); ir 1731 cm^{-1}; nmr ($CDCl_3$) τ 4.2–4.4 (1 H, m), 5.1–5.3 (2 H, m), and 6.6–8.5 (9 H, m); *m/e* 138. *Anal.* Calcd for $C_9H_{12}O$: C, 79.43; H, 8.82. Found: C, 79.20; H, 8.68.

Irradiation of **2** and excess of 1,3-cyclooctadiene for 3 hr gave 56% of a colorless oil: bp 105–108° (0.3 mm); ir 1729 cm^{-1}; nmr (CCl_4) τ 4.2–4.4 (2 H, m) and 6.7–8.3 (14 H, m); *m/e* 190 (parent). Analysis on column C showed three components of relative areas 15:62:23.

Similarly, irradiation for 3 hr of **2** (3.0 g) and furan (100 ml) gave an adduct mixture, bp 78–80° (0.4 mm), ir (film) 1741 cm^{-1}, which appeared to consist of both [2 + 2] and [4 + 2] adducts, as shown from the nmr spectrum [*inter alia*, τ 3.62 (t, J = 1.4 Hz, vinyl H of [4 + 2] adduct), 4.80 (t, J = 2.8 Hz, -CH=CHO- of [2 + 2] adduct), and 5.0 and 5.1 (s, m, -CHO- of [4 + 2] adduct)]. As with the products from **1** and furan, the temperature required for gas chromatographic purification caused cycloreversion of the [4 + 2] adduct and at least partial decomposition of the [2 + 2] adduct(s).

Analysis was feasible, at least, and there appear to be present three components, of areas ~ 5:4:1. Even with partial decomposition occurring, enough of the major [2 + 2] adduct was collected for infrared spectral comparison of its hydrogenation product with the major product from **3** and 2,3-dihydrofuran, with which it proved to be identical, and thus must have structure **22**. The sample obtained in the latter fashion (66% yield) had ir (film) 1733 cm^{-1}; nmr ($CDCl_3$) τ 3.71 (1 H, t, J = 2.8 Hz), 4.80 (1 H, t, J = 2.8 Hz), 5.1 (1 H, m), and 6.8–8.2 (7 H, m); mass spectrum *m/e* (rel intensity) 166 (parent, 6.5) and 68 (100). *Anal.* Calcd for $C_9H_{10}O_2$: C, 72.04; H, 6.64. Found: C, 71.88; H, 6.50.

Photochemical Reaction of 1 with Thiophene. A solution of **1** (1.5 g) in thiophene (110 ml) was irradiated for 10 hr. Evaporation of the excess thiophene and distillation gave 0.42 g of material, bp 81–90° (0.2 mm), as well as 0.89 g of enone dimers, bp 115–125° (0.2 mm). Two fractional distillations of the first fraction through a micro wire-spiral column gave 0.18 g (8%), bp 85–88° (0.2 mm), of **16**: nmr ($CDCl_3$) τ 3.84 (1 H, d, J = 5.4, J' = 1.6 Hz), 4.40 (1 H, 2 d, J = 5.4, J' = 2.6 Hz), 5.73 (1 H, 2 d, J = 8.0, J' = 5.4 Hz), and 6.8–8.6 (9 H, m); ir (film) 1705 (s) and 1600 (w) cm^{-1}; mass spectrum *m/e* (rel intensity) 180 (parent, 15), 97 (20), 84 (100). and 55 (76). *Anal.* Calcd for $C_{10}H_{12}OS$: C, 66.70; H, 6.62. Found: C, 66.45; H, 6.51.

Photochemical Addition of 1 to 2,5-Dimethylthiophene. A solution of **1** (2.0 g) and 2,5-dimethylthiophene (20 g) in benzene (100 ml) was irradiated through Pyrex for 3 hr. Evaporation of the solvent and excess 2,5-dimethylthiophene, followed by fractional distillation of the residue, gave crude **17**. Two more distillations gave **17** as a colorless oil: bp 112–114° (0.1 mm) (2.1 g, 51%); ir (film) 1699 cm^{-1}; nmr ($CDCl_3$) τ 4.72 (1 H, m), 6.7 (1 H), 8.1 (2 H, d, allyl CH_3), 8.50 (3 H, s), 8.50 (s), and 7.0–8.4 (7 H, m); mass spectrum *m/e* (rel intensity) 208 (parent, 16), 193 (35), and 110 (100). *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 69.25; H, 7.81. Found: C, 69.58; H, 7.55. Analysis on column A showed two incompletely resolved peaks in a ratio of ~ 2:1.

Photochemical Reaction of 1 with 1-Methylpyrrole. A solution of **1** (3.0 g, 0.03 mol) and 1-methylpyrrole (25 g) in benzene (100 g) was irradiated for 5 hr. Work-up in the usual manner gave, besides 1.4 g of recovered **1**, a golden oil, bp 80–95° (0.1 mm) (0.86 g), which darkened on standing in the presence of air: ir (film) 1700 cm^{-1} (s, br); nmr (CCl_4) τ 3.8 (1 H, m, br), 4.3 (1 H, m, br), 6.5 (3 H, 2 s, NCH_3), 6.7–8.3 (8 H, m).

Reaction of Carbostyril (15) with Furan. A solution of carbostyril (2.0 g, 13 mol) and furan (100 ml) in 95% ethanol (100 ml) was irradiated through Pyrex for 10 hr. Filtration of the suspension, after evaporation of excess furan, gave 47% of the known photodimer of carbostyril, mp 300–302°. Evaporation of the filtrate under reduced pressure gave a yellow semisolid residue which was chromatographed on a 25 × 300 nm column of silica gel. Elution with chloroform (500 ml) and 10:1 chloroform–ethyl acetate (700 ml) gave in the earlier fractions 0.96 g (75 ml each) of adduct **19** as an off-white solid, and in the later fractions 48% of unchanged **15**. Recrystallization of the combined product fractions from ethyl acetate–hexane gave pure **19** as white prisms: mp 201–202° (0.43 g, 37% based on unrecovered **15**); ir (KBr) 1663 (C=O) and 1594 cm^{-1} (vinyl ether); nmr ($CDCl_3$) τ 1.12 (1 H, br, NH), 2.9–3.1 (4 H, m), 3.60 (1 H, 2 d, J = 2.7, J' = 1.1 Hz), 4.68 (1 H, t, J = J' = 2.7 Hz), 4.85 (1 H, d of m, J = 7.4 Hz), 6.28 (2 H, br, s), 6.51 (1 H, 2 t, J = 7.4, J' = 1.5 Hz); mass spectrum *m/e* (rel intensity) 213 (parent, 0.5), 145 (61), 90 (80), and 68 (100). *Anal.* Calcd for $C_{13}H_{11}O_2N$: C, 73.24; H, 5.16. Found: C, 72.95; H, 5.30. Shaking a sample of **19** (0.10 g) in ethyl acetate (40 ml) with 10% palladium on charcoal under 1 atm pressure of hydrogen for 8 hr, followed by filtration of the catalyst and evaporation of the solvent, gave dihydro-**19** as white needles, mp 194–195° after recrystallization from ethyl acetate–hexane: ir 1671 (C=O, s), 1598 cm^{-1} (w); nmr ($CDCl_3$) τ 1.02 (1 H, br), 2.7–3.1 (4 H, m), 4.9 (1 H, m), 5.48 (2 H, m), 6.93 (1 H, m), 7.0–7.8 (5 H, m).

Photochemical Addition of 15 to 2,3-Dihydrofuran. A solution of **15** (1.0 g) and 2,3-dihydrofuran (20 g) in ethanol (200 ml) was irradiated through Pyrex for 6 hr. Evaporation of the ethanol and excess olefin gave a semisolid residue which was chromatographed on silica gel. Elution with 10:1 chloroform–ethyl acetate gave first four fractions containing crude **20** and, later, unchanged **15** (0.08 g). Recrystallization of the crude **20** from ethyl acetate–hexane gave the pure material as white leaflets: mp 174–175°; ir (KBr) 1660, 1592, 1410 cm^{-1}; nmr ($CDCl_3$) τ 2.7–3.0 (4 H, m), 4.8 (1 H, m), 5.6 (2 H, m), 6.4 (1 H, s, br), 6.8 (1 H, m), and 7.0–7.9 (5 H, m). *Anal.* Calcd for $C_{13}H_{13}NO_2$: C, 72.58; H, 6.04. Found: C, 72.69; H, 5.86.

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Registry No.—**1**, 930-68-7; **2**, 930-30-3; **3**, 51519-59-6; **4**, 51519-60-9; **5** isomer 1, 51519-61-0; **5** isomer 2, 51519-62-1; **5** isomer 3, 51519-64-3; **6**, 51519-65-4; **7**, 51519-66-5; **8a**, 51519-67-6; **8b**, 51519-68-7; **9**, 51567-37-4; **10**, 51519-69-8; **13**, 51519-70-1; **15**, 493-62-9; **16**, 51567-38-5; **17**, 51519-71-2; **18**, 51519-72-3; **19**, 51519-73-4; dihydro-**19**, 51519-74-5; **20**, 51519-75-6; **21**, 51519-76-7; **22**, 51519-77-8; 2,3-dihydrofuran, 1191-99-7; thiophene, 110-02-1; 2,5-dimethylthiophene, 638-02-8; 1-methylpyrrole, 96-54-8; cyclohexenone–1,3-cyclohexadiene adduct A, 51519-78-9; cyclohexenone–1,3-cyclohexadiene adduct B, 51519-79-0; 1,3,5-cycloheptatriene dimer, 31510-69-7; cyclohexenone–cycloheptatriene adduct, 51519-81-4; cyclohexenone–1,3-cyclooctadiene adduct A, 51519-82-5; cyclohexenone–1,3-cyclooctadiene adduct B, 51519-83-6; *trans*-cyclohexenone–1,5-cyclooctadiene adduct, 51519-84-7; *cis*-cyclohexenone–1,5-cyclooctadiene adduct, 51607-06-8; 2-cyclopentenone–1,3-butadiene adduct A, 51519-85-8; 2-cyclopentenone–1,3-butadiene adduct B, 51519-86-9.

References and Notes

(1) (a) Preliminary communication: T. S. Cantrell, *Chem. Commun.*, 1656 (1970). (b) Address correspondence to The American University.

(2) For reviews, see (a) P. E. Eaton, *Accounts. Chem. Res.*, **1**, 50 (1968); (b) P. de Mayo, *ibid.*, **4**, 41 (1971).

(3) (a) P. de Mayo, J. P. Pete, and M. F. Tchir, *J. Amer. Chem. Soc.*, **89**, 5712 (1967); (b) O. L. Chapman, T. H. Koch, F. Klein, P. J. Nelson, and E. L. Brown, *ibid.*, **90**, 1657 (1968); (c) P. de Mayo, J. P. Pete, and M. F. Tchir, *Can. J. Chem.*, **46**, 2535 (1968); (d) P. J. Wagner and D. Bucheck, *J. Amer. Chem. Soc.*, **91**, 5090 (1969); (e) P. De Mayo, A. A. Nicholson, and M. F. Tchir, *Can. J. Chem.*, **48**, 225 (1970).

(4) (a) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); (b) T. S. Cantrell, W. S. Haller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969); (c) T. S. Cantrell, *Tetrahedron*, **27**, 1227 (1971).

(5) (a) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965, p 207; (b) O. L. Chapman and G. Lenz in "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967, p 297.
(6) (a) See, for example, P. J. Wagner and G. S. Hammond, *Advan. Photochem.*, **5**, 21 (1968); (b) *ibid.*, **5**, 79 (1968).
(7) W. H. Hardham and G. S. Hammond, *J. Amer. Chem. Soc.*, **89**, 3400 (1967).
(8) G. O. Schenck, J. Kuhls, and C. H. Krauch, *Justus Liebigs Ann. Chem.*, **693**, 20 (1966).
(9) K. Kraft, G. Koltzenburg, and G. O. Schenck, *Tetrahedron Lett.*, 353 (1965).
(10) (a) T. Kubota, K. Shima, S. Toki, and H. Sakurai, *Chem. Commun.*, 1462 (1969); (b) J. A. Barltrop and H. A. J. Carless, *ibid.*, 1637 (1970).
(11) J. A. Barltrop and H. A. J. Carless, *J. Amer. Chem. Soc.*, **93**, 4237 (1971).
(12) D. I. Schuster and D. I. Sussman, *Tetrahedron Lett.*, 1657 (1970).
(13) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.
(14) P. E. Eaton, *J. Amer. Chem. Soc.*, **84**, 2448 (1962).
(15) (a) Cyclopentenone dimers: P. E. Eaton, *J. Amer. Chem. Soc.*, **84**, 2344 (1962). (b) Cyclohexenone dimers: E. Y. Y. Lam, D. Valentine, and C. S. Hammond, *ibid.*, **89**, 3482 (1967).
(16) W. L. Dilling, *et al.*, *J. Amer. Chem. Soc.*, **92**, 1399 (1970).
(17) R. S. H. Liu, *J. Amer. Chem. Soc.*, **89**, 112 (1967).
(18) (a) R. Dowbenko, *Tetrahedron*, **20**, 1843 (1964); (b) L. Friedman, *J. Amer. Chem. Soc.*, **86**, 1885 (1964).
(19) (a) P. K. Corver, P. J. van der Haak, N. Steinberg, and T. J. de Boer, *Recl. Trav. Chim. Pays-Bas*, **84**, 129 (1965); (b) T. S. Cantrell, *J. Org. Chem.*, **39**, 2242 (1974).
(20) C. Rivas, M. Veluz, and O. Crescente, *Chem. Commun.*, 1474 (1970).
(21) G. Evanega and D. L. Fabiny, *J. Org. Chem.*, **35**, 1757 (1970).
(22) (a) G. O. Schenck, W. Hartmann, and R. Steinmetz, *Chem. Ber.*, **96**, 498 (1963); (b) G. R. Evanega and E. B. Whipple, *Tetrahedron Lett.*, 4783 (1966); (c) E. B. Whipple and G. R. Evanega, *Tetrahedron*, **24**, 1299 (1968).
(23) P. J. Wagner and D. Bucheck, *J. Amer. Chem. Soc.*, **91**, 5090 (1969).
(24) M. A. Gianturco, P. Friedel, and G. Flanagan, *Tetrahedron Lett.*, 1847 (1965).

Cycloaddition of 1-Azirines with Cyclopentadienones. Formation of 2*H*- and 3*H*-Azepines, and Mechanistic Interpretation[1,2]

Alfred Hassner* and David J. Anderson

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

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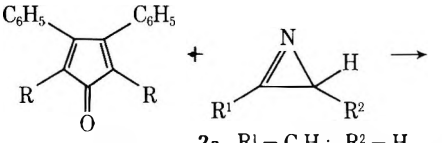
Cyclopentadienones **1** and 1-azirines **2** react in refluxing toluene to afford 3*H*-azepines **3** directly, with loss of CO. Azirines **2** react similarly with 1,3-diphenylinden-2-one (**16**) and phencyclone (**17**) to give 2*H*-azepines **18** and **19**. The phenanthro-2*H*-azepines **19** rearrange under basic or thermolytic conditions to the more stable 3*H* isomers with the ring proton at the 9 position of the phenanthrene nucleus. Analogous cycloadditions of **16** and **17** with 1,2,3-triphenylcyclopropene (**22**) lead to cycloheptatrienes and exo bridging carbonyl compounds. The mechanism of azepine formation is rationalized in terms of an *endo*-2-azatricyclo[3.2.1.$0^{2,4}$]oct-6-en-8-one intermediate (**13**) which extrudes CO with disrotatory ring opening of the aziridine C–N bond, to afford primarily 2*H*-azepines which may or may not then rearrange to the 3*H* isomers. Analysis of the nmr spectra, with particular attention to the conformational preference of the azepine ring, is also recorded.

During the last decade 1-azirines have become readily available and their synthetic utility has been extensively developed.[3] Recently the first cycloadditions of these heterocyclic systems have been reported. These include thermal reactions with ketenes,[4,5] ketenimines,[5] nitrile oxides,[6] cyclopentadienones,[2,7] cyclopentadiene,[8] diphenylisobenzofuran,[9] and diazomethane[10] to yield a variety of products. 1-Azirines also react photochemically (*via* the nitrile ylide) with themselves,[11–13] as well as with various carbon–carbon[14,15] and hetero double bonds.[15,16]

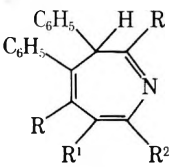
The synthesis and chemistry of azepines has likewise evolved largely during the last decade.[17] Although a number of examples of N-substituted 1*H*-azepines are known,[17] attempts to prepare the unsubstituted system have led to the formation of 3*H*-azepines.[18] 4*H*-Azepines rearrange under thermal or basic conditions to the 3*H* isomers.[19–22] No example of the 2*H*-azepine was known prior to this study.[2] This has led to the generalization[21] that the relative stabilities of the azepine systems are in the order 2*H* < 4*H* < 3*H*. It has also been calculated[23] that for the parent systems, 1*H*-azepine has a resonance energy of −1.80 kcal mol^{-1}, whereas that of the 3*H*-azepine is +0.23.

We report here our detailed findings on the reaction of 1-azirines with a variety of cyclopentadienones to give 2*H*- and 3*H*-azepines.

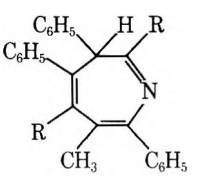


1a, R = C_6H_5
b, R = CH_3
c, R = C_2H_5

2a, $R^1 = C_6H_5$; $R^2 = H$
b, $R^1 = C_6H_5$; $R^2 = CH_3$
c, $R^1 = R^2 = C_6H_5$
d, $R^1 = C_6H_5$; $R^2 = CH_2OH$
e, $R^1 = C_6H_5CH_2$; $R^2 = H$



3a, $R = R^1 = C_6H_5$; $R^2 = H$
b, $R = R^1 = C_6H_5$; $R^2 = CH_3$
c, $R = R^1 = R^2 = C_6H_5$
d, $R = R^1 = C_6H_5$; $R^2 = CH_2OH$
e, $R = C_6H_5$; $R^1 = C_6H_5CH_2$; $R^2 = H$
f, $R = CH_3$; $R^1 = C_6H_5$; $R^2 = H$
g, $R = R^2 = CH_3$; $R^1 = C_6H_5$
h, $R = CH_3$; $R^1 = R^2 = C_6H_5$
i, $R = CH_3$; $R^1 = C_6H_5CH_2$; $R^2 = H$
j, $R = C_2H_5$; $R^1 = C_6H_5$; $R^2 = H$
k, $R = C_2H_5$; $R^1 = C_6H_5$; $R^2 = CH_3$



4a, R = C_6H_5
b, R = CH_3

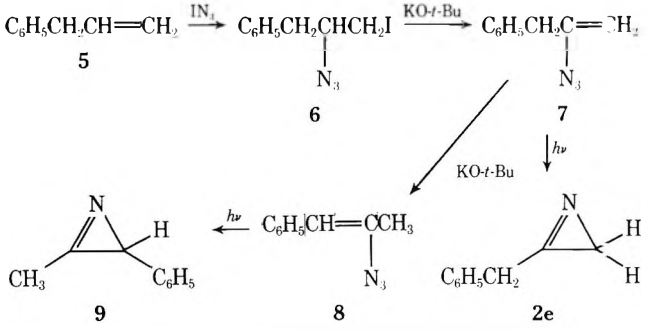
Results and Discussion

Though no reaction occurs between tetracyclone (**1a**) and azirine **2b** in refluxing benzene overnight, clean conversion into an azepine **3b** with loss of CO takes place in refluxing toluene after 4 days.[2] The structural assignment to 3*H*-azepines **3** was facilitated by the use of dimethylcyclone (**1b**) and 2-phenylazirine (**2a**) as substrates. The resulting azepine **3f**, produced in 86% yield, displayed two methyl singlets at τ 8.24 and 7.72, the latter exhibiting

homoallylic coupling[24,25] (J = 0.8 Hz) to the 7-proton (broad singlet at 3.06), absence of NH absorption and absence of the low-field two-proton multiplet characteristic of the PhC=N– system in the tetracyclone adducts. This eliminated positions 1, 2, 5, and 7 (in formula **3**) as the site of attachment for the proton derived from the azirine ring (*e.g.*, **2b**). An nmr singlet for the benzylic protons in **3e** or **3i** derived from 2-benzylazirine (**2e**) left for consideration only the 3*H*-azepine structure **3** or an isomeric 4*H*-azepine. The mass spectral fragmentation pattern of the azepine products showed the major pathway as loss of the RC≡N moiety. When the 2-methyl group was deuterated, this loss was represented by $CD_3C{\equiv}N$, confirming the 3*H*-azepine (**3**) assignment.

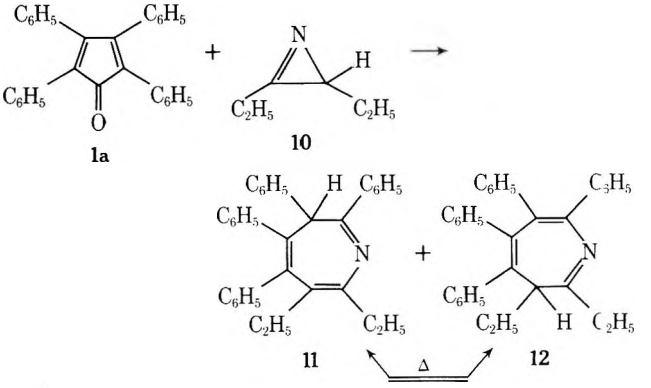
In addition to the isolation of azepine **3i** from the reaction of 2-benzyl-1-azirine (**2e**) and **1a** or **1b**, minor products, shown to be the isomeric **4a** and **4b**, were also obtained. The source of **4a** was not phenyl migration in benzyl azepine **3i**, but the synthetic pathway[26,27] used in the formation of azirine **2e** (Scheme I). We were able to show that vinyl azide 8 was produced by base promoted isomerization of **7** even during the very short (10 min) dehydroiodination of **6** and that its photolysis product **9** reacted with tetracyclone **1a** to afford **4a**.

Scheme I



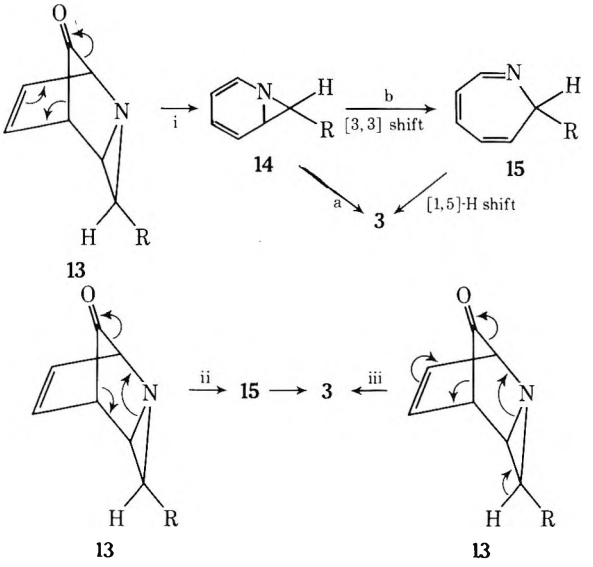
In subsequent preparative procedures 2-aryl-1-azirines could be generated *in situ* from the corresponding vinyl azides. The vinyl azide was first decomposed in refluxing toluene and the dienone then added. This technique removed the task of preparing and handling the obnoxious smelling 1-azirines.

Although no thermally allowed [1,5]-hydrogen shifts were observed on the 3*H*-azepines **3**, such a process was detected on heating **11** or **12** in xylene. The same equilibrium mixture (8:3) was produced on refluxing **10**[27] with **1a** for 10 days. The structure of **12** was obvious from its nmr spectrum which displayed a triplet at τ 5.87 (H-3), and a H_AH_B pattern for the methylene protons of the 2-ethyl group, which underwent slow exchange with D_2O at room temperature.



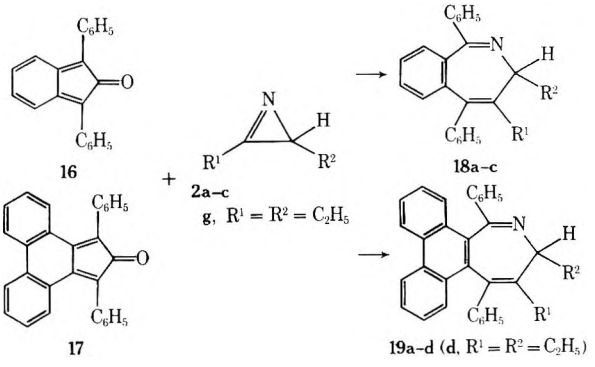
Mechanism. The formation of azepines **3** from azirines **2** and cyclopentadienones, resulting in the 2 and 3 substituents of the azirine being placed at C-6 and C-7, indicated that rupture of the azirine C=N bond had occurred[28] during cycloaddition and one was therefore dealing with a Diels–Alder addition. This is also consistent with the failure of 3,3-dimethyl-2-phenyl-1-azirine[29] and 3-carbomethoxy-2-phenyl-1-azirine[27,30] to react with **1a** or **1b**.

If the assumption is made that 1-azirines and cyclopentadienones first react in a [4 + 2] fashion to give an endo intermediate **13** (see below), then three possible routes are available to account for the subsequent formation of 3*H*-azepines. Mechanism i involves loss of carbon monoxide



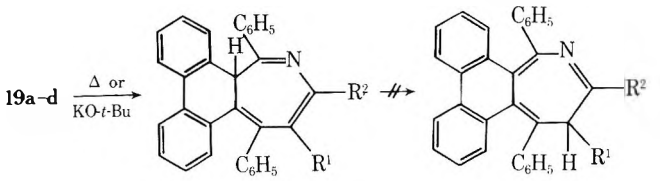
from **13** through involvement of the C=C bond to afford the azanorcaradiene **14**. The latter can either undergo ring opening (path a) to give the 3*H*-azepine **3** or a disrotatory electrocyclic rearrangement (path b) to produce the 2*H*-azepine **15** which rearranges *via* a thermally allowed [1,5]-hydrogen shift to give the thermodynamically more stable **3**. In mechanism ii, CO is lost *via* participation of the aziridine carbon–nitrogen bond to afford **15** which rearranges to **3** as above. Mechanism iii utilizes a concerted hydrogen migration with loss of carbon monoxide from **13** to yield **3** directly. Acceleration for the analogous process in the decarbonylation of tricyclooctenones is well established.[31]

Routes i and iii differ from ii inasmuch as they both require participation of the carbon–carbon double bond of **13** in the primary step for azepine formation. If this double bond were rendered less available (*i.e.*, requiring destruction of aromatic resonance), then route ii should be favored. Indeed, when 1,3-diphenylinden-2-one **16**[32] and phencyclone **17**[32] were chosen as the dienone components, in the reaction with azirines **2a–c** and **2g** in refluxing xy-



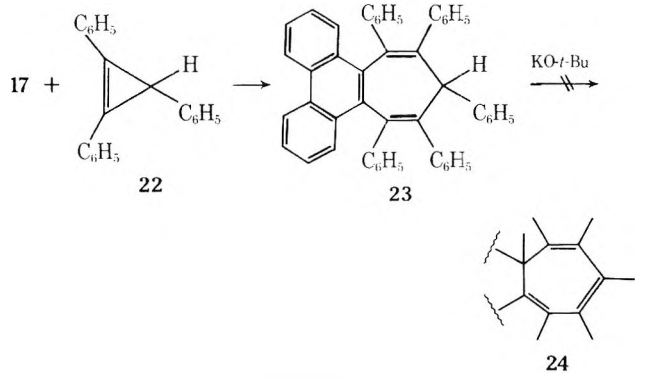
lene[33] and toluene, respectively, highly crystalline products **18a–c** and **19a–d** were rapidly formed. The reaction times of **16** and **17** with azirines indicated that phencyclone had comparative reactivity to the dimethylcyclone **1b** (in toluene) and that the indenone **16** was five to six times as reactive as **1b** (in xylene).

The adducts **19,** which showed the expected low-field [τ ($CDCl_3$) 1.45–1.20] two-proton multiplet attributable to the ortho hydrogens on PhC=N, were found to isomerize in high yield, on treatment with potassium *tert*-butoxide in refluxing dimethoxyethane or upon thermolysis at *ca.* 200°.



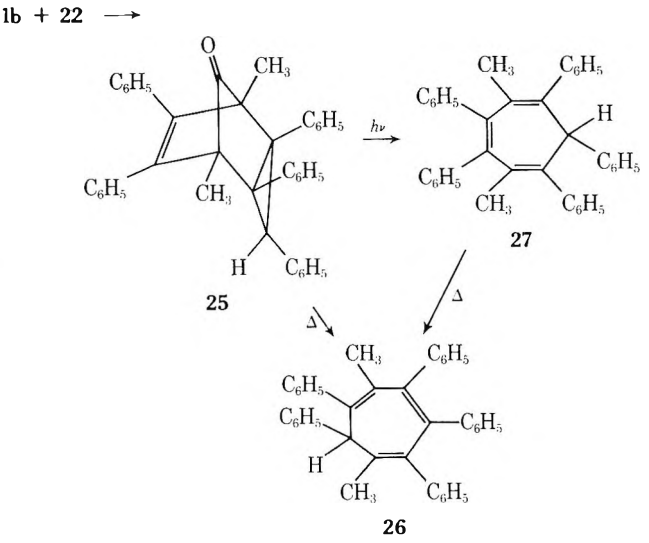
The products **20a–d** exhibited a one-proton singlet in the region τ ($CDCl_3$) 4.35–3.67. The isomeric 3*H*-formula **21,** produced by a [1,5]-hydrogen shift of **20,** was eliminated by the absence of coupling of the ring proton of **20d** ($R^1 = R^2 = C_2H_5$) with the ethyl group. Products **20a–d** all displayed a four-proton multiplet at τ ($CDCl_3$) 1.70–0.95, tentatively ascribed to the ortho protons of the 2- and 5-phenyl groups. The latter falls within the deshielding region of the phenanthrene nucleus. Due to the higher resonance energy of a benzene ring (as in **18**) *vs.* the center ring of a phenanthrene (as in **19**), 2*H*-azepines **18** did not undergo rearrangement under similar reaction conditions that effected the transformations **19** → **20.**

For the reaction **19** → **20** to proceed, it is evident that the difference in energy parameters of the 2*H*- and 3*H*-azepines must be greater than the comparable parameters of the center ring of the phenanthrene nucleus. Some support of this proposal is provided by the fact that the cycloheptatriene **23** [prepared from phencyclone **17** and 1,2,3-triphenylcyclopropene (**22**)] did not isomerize to **24** under the basic conditions employed for **19** → **20.** In the acecyclone series[34] the analog of **23** was more stable than that of **24.**

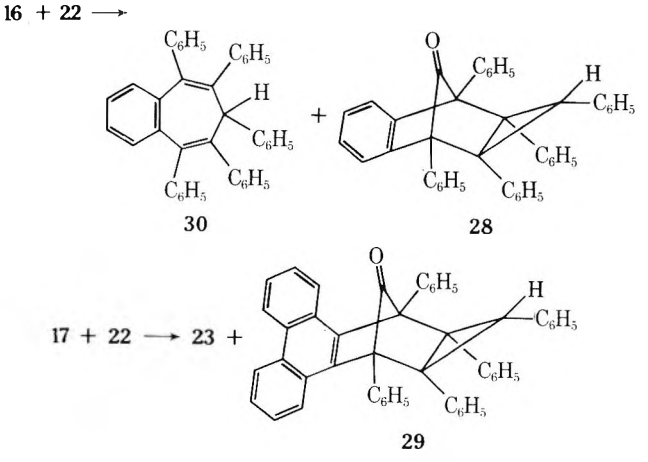


Additional evidence to substantiate the mechanism of azepine formation comes from the cycloaddition of cyclopropenes to cyclopentadienones. In analogy with previous studies,[30,35] bridged ketonic intermediate **25** [ν_{max} (KBr) 1760 cm^{-1}] was isolable on heating **22** with **1b** in benzene for 4 hr. The nmr spectrum of **25** displayed equivalent methyl groups at τ 9.11 and a one-proton singlet at 7.13.

When **25** was heated under reflux in toluene or xylene, it smoothly lost CO and the unsymmetrical cycloheptatriene **26** was formed (nonequivalent methyl groups at τ 8.80 and 8.16 and the ring proton at 5.18). The initial interpretation[2a] invoked a mechanism similar to ia, but this was revised[2b] since photochemical decarbonylation of **25** produced the symmetrical cycloheptatriene **27** (equivalent methyl groups at τ 8.25 and the ring proton at 5.00) which rearranged on heating to **26.**



It is well established that the presence of a fused endo cyclopropane ring in the β positions to bridging carbonyl[35] and azo[36] compounds greatly accelerates the extrusion of carbon monoxide and nitrogen from these molecules, due to more efficient orbital overlap in the transition states. Hence, we believe that **13** has the endo configuration and that the electron pair on the aziridine N facilitates the loss of CO. Support for this proposal comes from the isolation of the exo ketones **28** and **29** (ν_{max} 1776 cm^{-1}) in addition to the cycloheptatrienes **30** and **23.** The endo ketones would be expected to decompose readily to afford **30** and **23,** but the exo isomers **28** and **29** were stable up to 300°.



Regiochemistry. The regiochemistry of the azirine cycloaddition reaction was also examined, using the unsymmetrical dienone **31.** Formally the 3*H*-azepines **32** and **33** are expected from this reaction, their relative amounts depending on the electronic nature of the azirine carbon–nitrogen double bond and the steric factors involved in the addition. The ratios of **32:33** (see Table I) were determined by nmr integration of the crude reaction mixture and separation was accomplished by fractional crystallization and chromatography. If the azirine double bond and the dienone are polarized as shown, then azepines **32** should be the predominant products (if steric control is unimportant). This is indeed the case when phenylazirine **2a** is employed. The use of *p*-methoxyphenylazirine **2f** causes an increase in the ratio of **32:33** as anticipated. However,

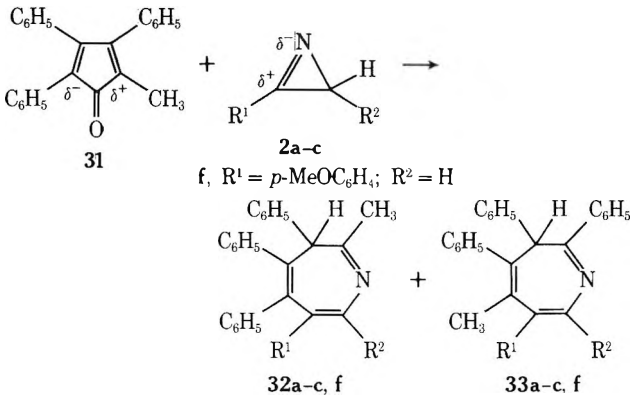
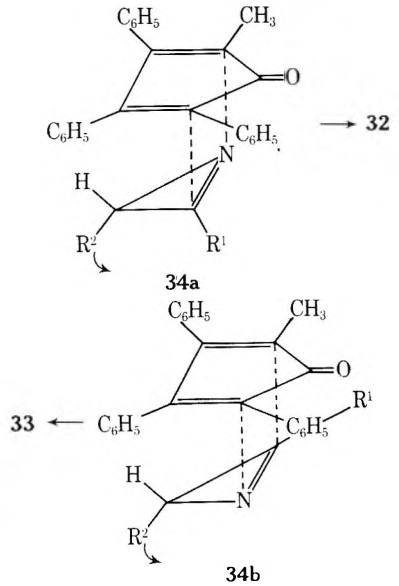


Table I
Ratio of 3*H*-Azepine 32:33 Formed in the Cycloaddition of 30 to 2

	32	33
a	2	1
b	1	1.4
c	1	6
f	5	1

when the 3-substituted azirines **2b** and **c** were used a reversal of the product ratios occurred. The reasons for this were not immediately apparent since the changes in azirine substituents do not occur at the reactant centers. It may tentatively be ascribed to a "weighting" effect of the azirine ring induced by the 3 substituent, the introduction of which causes a decrease in efficiency of the azirine ring to achieve coplanarity with the dienone in the endo transition states **34a** and **b**. This effect manifests itself by a tilting downwards of the azirine ring about the C=N bond, and an increased interaction of the azirine 2-aryl substituent with the 2 and 5 substituents of the dienone. Clearly if this is the case, then **34b** will be favored since it involves an aryl–methyl interaction compared to the aryl–phenyl one of **34a**. The observed results support this hypothesis.



Of interest is the fact that the physical properties of 3*H*-azepine **32c** ($R^1 = R^2 = C_6H_5$) [pale yellow crystals, mp 206°; τ ($CDCl_3$) 7.76 (s, 3 H), 4.36 (s, 1 H), 3.50–2.50 (m, 25 H)] are similar to those of an alleged[7] 4*H*-azepine [pale yellow crystals, mp 198–201°; τ ($CDCl_3$) 7.80 (s, 3 H), 4.39 (s, 1 H), 3.32–2.67 (m, 25 H)] isolated in minor yield from tetracyclone **1a** and 3-methyl-2-phenylazirine (**2b**). It is proposed that the 4*H* structure is incorrect and that this compound is in fact the 3*H*-azepine **32c**. This is conveniently explained by assuming a [1,5]-hydrogen shift of the major product of the reaction, namely the 3*H*-azepine **3b**. As a generalization, it should be noted that the observed *[1,5]-hydrogen shifts in the isomerization of azepines always proceeded in the direction of the C=N rather than in the direction of the N=C bond, e.g.*, **11** ⇄ **12**, **19** → **20**, **3b** → **32c**.

Nmr Spectra. The chemical shifts of the 3*H*-ring proton in the azepines studied reveal some interesting trends. The 3*H* in the tetracyclone derived series (τ 3.6–3.9 in **3a–e**, **5a**, **11**) is shifted downfield by *ca.* 65 Hz compared to azepines derived from the 2,5-dialkylcyclones **1b,c** with the same azirines (τ 4.7–4.85 in **3f–i**, **5b**). This is not taken to indicate a change of conformation of the azepine ring but a deshielding effect of the 2-phenyl group. In a not too dissimilar model system **35**, the benzhydrilic proton is shifted downfield by *ca.* 56 Hz on changing R = CH_3[37] to R = C_6H_5.[38]

$(C_6H_5)_2CHCOR$
35a, R = CH_3
b, R = C_6H_5

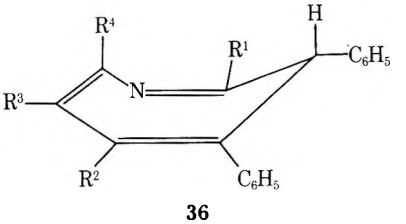
The mean position of the proton in the series derived from the unsymmetrical cyclone **31**, compared to the analogous 2,5-dimethylazepines, experiences a shift downfield of *ca.* 22 Hz for $R^1 = CH_3$ and an upfield shift of *ca.* 13 Hz when $R^1 = C_6H_5$. Consequently, the introduction of a 5-phenyl substituent on the azepine ring increases the deshielding mechanisms experienced by the 3*H* proton. Furthermore the substitution of methyl groups at the 2 and 5 positions by phenyl groups causes a shift downfield of *ca.* 30 Hz of the 7 proton.

Homoallylic coupling, verified by spin decoupling, was observed in **3f** between the 2-CH_3 and the 7-H (J = 0.8 Hz). This coupling disappeared in the 2-CD_3 analog and was found to be general for a 2-alkyl group and a 7 proton. It was interesting that this occurred through the nitrogen atom, since previously observed[39,40] homoallylic coupling in 3*H*-azepines did not involve the nitrogen atom. Examples are known though involving a heteroatom.[24,25] In all 2-phenyl-substituted azepins, the two ortho protons of the PhC=N– system absorb at lower field (*ca.* 0.5 ppm lower) than the other aromatic protons.

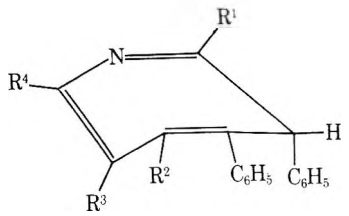
The appearance of the methylene protons of the 2-ethyl group of **12** as an AB pattern is consistent with restricted rotation and proximity to a chiral center (C-3). As expected the 3*H* appeared as a triplet (J = 7.5 Hz). A similar observation has been made for a 2-ethoxy group.[39] An unexpected result was the AB pattern (J = 13 Hz) for the methylene protons of the $-CH_2OH$ group in the 7 position of **3d**. These were broadened by the –OH, but deuterium exchange caused the signals to be well resolved.

Similarly we observed an ABX pattern for the parent azirine **2d** (J_{AB} = 12.5 Hz, J_{AX} = 3.0 Hz, J_{BX} = 4.7 Hz). These results probably indicate a preferred conformation in solution.

Conformations of Azepines. It is reasonable to assume[7] that of the two possible conformations of the 3*H*-azepine ring **36** and **37**, the thermodynamically more stable one, **36**,



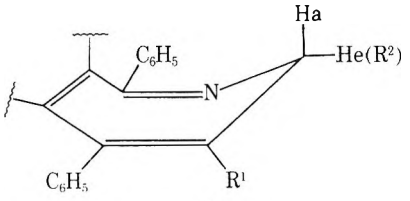
36



37

has the 3*H* proton in the axial position and the 3-phenyl group equatorial.

It is significant that in the benzo- and phenanthro-2*H*-azepines **18a** and **19a**, the ring protons were coupled (J = 10 and 9 Hz, respectively), indicating slow ring inversion on the nmr time scale. The lower field doublets were assigned[41] to the equatorial proton and the higher doublets to the axial proton in conformer **38**. When the 2 position



38

was substituted by a methyl group (**19b** and **20b**), then the higher field signal for the axial ring proton remained at approximately the same chemical shift, indicating that the methyl group occupied the equatorial position. A phenyl group at position 2 would also be expected to be equatorial. When the 2 group was ethyl, then the ring proton exhibited a pattern characteristic for X of an ABX system, indicative of restricted rotation of the 2-ethyl group and its attachment to a chiral center.

The nmr data of the phenanthro-3*H*-azepines **20** display the ring proton at approximately the same position as in the tetracyclone-derived 3*H*-azepines. There is considerable driving force for this proton to occupy the axial position since in this conformation the planarity of the phenanthrene nucleus is maintained, unlike in the other conformation. This substantiates the assumption of **36** as the most stable conformation of the simple 3*H*-azepines.

Experimental Section[42]

General Procedure for the Preparation of 3*H*-Azepines[43] from Cyclones 1a,b,c. The cyclopentadienone (5 mmol) and the azirine (6 mmol) were heated under reflux in toluene (15 ml) in an atmosphere of nitrogen until tlc indicated that all the dienone had reacted. (Times are indicated in the text.) The solvent was removed *in vacuo* and the residue either recrystallized directly or chromatographed over Woelm neutral alumina (activity I), as indicated in the text.

2,3,4,5,6-Pentaphenyl-3*H*-azepine (3a) was isolated from **1a** and **2a** after 4 days, by recrystallization from ethanol as golden yellow crystals (87%): mp 212°; nmr τ 2.48 (4-H), 3.62 (3-H).

Anal. Calcd for $C_{36}H_{27}N$: C, 91.3; H, 5.75. Found: C, 91.4; H, 5.9.

7-Methyl-2,3,4,5,6-pentaphenyl-3*H*-azepine (3b) was isolated directly from **1a** and **2b** after 6 days, by recrystallization from ethanol as yellow hexagonal plates (65%): mp 212°; nmr τ 8.23 (7-CH_3), 3.77 (3-H).

Anal. Calcd for $C_{37}H_{29}N$: C, 91.1; H, 6.0. Found: C, 91.0; H, 6.0.

2,3,4,5,6,7-Hexaphenyl-3*H*-azepine (3c) was obtained from **1a** and **2c** after 12 days, by chromatography using ether–petroleum (1:3) eluent, as pale yellow crystals from ethanol (61%): mp 227°; nmr τ 3.62 (3-H).

Anal. Calcd for $C_{42}H_{31}N$: C, 91.8; H, 5.7. Found: C, 91.5; H, 5.7.

7-Hydroxymethyl-2,3,4,5,6-pentaphenyl-3*H*-azepine (3d) was obtained from **1a** and **2d** after 6 days as lemon yellow granules (55%) from ethanol: mp 213°; nmr τ 7.4 (OH), 3.6 (3-H).

Anal. Calcd for $C_{37}H_{29}NO$: C, 88.2; H, 5.8. Found: C, 88.0; H, 5.7.

Tetracyclone (1a) and 2-Benzyl-1-azirine (2e). After 3 days' reflux, the residue was chromatographed. Elution with dichloromethane–pentane (1:30) afforded 6-methyl-2,3,4,5,7-pentaphenyl-3*H*-azepine (**4a**) (5%) as bright yellow needles: mp 177° from hexane; nmr τ 8.6 (6-CH_3), 3.83 (3-H).

Anal. Calcd for $C_{37}H_{29}N$: C, 91.1; H, 6.0. Found: C, 90.9; H, 6.0.

Continued elution with increasing amounts of dichloromethane in pentane afforded 6-benzyl-2,3,4,5-tetraphenyl-3*H*-azepine (**3e**) (51%) as bright yellow crystals from hexane: mp 161°; nmr τ 6.72 (6-CH_2), 2.74 (4-H), 3.8 (3-H).

Anal. Calcd for $C_{37}H_{29}N$: C, 91.1; H, 6.0. Found: C, 90.9; H, 6.0.

Tetracyclone (1a) and 2,3-Diethylazirine (10). The solvent was removed after 10 days' reflux and the residue chromatographed. Elution with dichloromethane–hexane (1:2) afforded a mixture (85%) of azepines. Two recrystallizations from ethanol afforded 6,7-diethyl-2,3,4,5-tetraphenyl-3*H*-azepine (**11**) as yellow needles: mp 151°; nmr τ 9.68 (t, J = 7.5 Hz, 6-Et), 8.01 (q, J = 7.5 Hz, 6-CH_2), 8.9 (t, J = 7.5 Hz, 7-Et), 7.79 (q, J = 7.5 Hz, 7-CH_2), 3.94 (3-H).

Anal. Calcd for $C_{34}H_{31}N$: C, 90.0; H, 6.9. Found: C, 90.1; H, 7.0.

Two recrystallizations of the combined filtrate material gave 2,3-diethyl-4,5,6,7-tetraphenyl-3*H*-azepine (**12**) as pale yellow flakes: mp 127°; τ ($CDCl_3$) 9.15–8.70 (m, 6 H), 8.70–8.25 (m, 2 H), 8.03–7.54 (m, 2 H), 5.87 (t, J = 7.5 Hz, 1 H), 3.40–2.50 (m, 20 H).

Anal. Calcd for $C_{34}H_{31}N$: C, 90.0; H, 6.9. Found: C, 89.9; H, 7.0.

2,5-Dimethyl-3,4,6-triphenyl-3*H*-azepine (3f) was obtained from **1b** and **1a** after 13 hr by recrystallization from hexane as tan crystals (86%): mp 123°; nmr τ 7.72 (d, J = 0.8 Hz, 2-CH_3), 8.24 (5-CH_3), 3.06 (7-H), 4.71 (3-H).

Anal. Calcd for $C_{26}H_{23}N$: C, 89.4; H, 6.6. Found: C, 89.5; H, 6.7.

In a large-scale preparation the vinyl azide (20.0 g, 0.138 mol) was first decomposed in toluene (250 ml) under reflux for 2 hr. The dienone (30.0 g, 0.115 mol) was added and the mixture heated under reflux for an additional 12 hr. Work-up afforded the azepine (33.9 g, 85%).

2,5,7-Trimethyl-3,4,6-triphenyl-3*H*-azepine (3g) was isolated from **1b** and **2b** as pale yellow flakes (83%) from ethanol: mp 182°; nmr τ 7.79 (2-CH_3), 8.42 (5-CH_3), 8.48 (7-CH_3), 4.82 (3-H).

Anal. Calcd for $C_{27}H_{25}N$: C, 89.2; H, 6.9. Found: C, 89.5; H, 7.0.

The azepine (88%) was also prepared *via* the vinyl azide as for **3f**.

2,5-Dimethyl-3,4,6,7-tetraphenyl-3*H*-azepine (3h) was obtained from **1b** and **2c** after 3.5 days by recrystallization from ethanol as pale yellow needles (63%): mp 189°; nmr τ 7.72 (2-CH_3), 8.36 (5-CH_3), 4.72 (3-H).

Anal. Calcd for $C_{32}H_{27}N$: C, 90.3; H, 6.4. Found: C, 90.6; H, 6.5.

1b and 2-Benzyl-1-azirine (2e). After 2 days' reflux the solvent was removed and the residue chromatographed. Ether–pentane (1:2) eluted 2,5,6-trimethyl-3,4,7-triphenyl-3*H*-azepine (**4b**) as pale yellow crystals (6%) from hexane: mp 181°; nmr τ 7.73 (2-CH_3), 7.99 (5-CH_3), 8.33 (6-CH_3), 4.85 (3-H).

Anal. Calcd for $C_{27}H_{25}N$: C, 89.2; H, 6.9. Found: C, 89.4; H, 6.9.

Elution with increasing amounts of ether in pentane afforded 6-benzyl-2,5-dimethyl-3,4-diphenyl-3*H*-azepine (**3i**) as pale yellow crystals (51%) from hexane: mp 90°; nmr τ 7.79 (2-CH_3), 8.1 (5-CH_3), 6.5 (CH_2), 3.17 (7-H), 4.77 (3-H).

Anal. Calcd for $C_{27}H_{25}N$: C, 89.2; H, 6.9. Found: C, 89.3, H, 6.7.

2,5-Diethyl-3,4,6-triphenyl-3*H*-azepine (3j) was obtained from **1c** and **2a** after 17 hr by chromatography (ether–hexane, 1:3) as a pale yellow oil (90%). The picrate crystallized as bright yellow needles from ethanol: mp 169°; nmr τ 8.8 (t, J = 7.5 Hz, 2-CH_3), 9.3 (t, J = 7.2 Hz, 5-CH_3), 7.35–8.04 (m), 2.96 (7-H), 4.78 (3-H).

Anal. Calcd for $C_{34}H_{30}N_4O_7$: C, 67.3; H, 5.0; N, 9.2. Found: C, 67.3; H, 5.0; N, 9.2.

2,5-Diethyl-7-methyl-3,4,6-triphenyl-3*H*-azepine (3k) was isolated from **1c** and **2b** as pale yellow crystals (66%): mp 113° from ethanol; nmr τ 8.76 (t, J = 7.5 Hz, 2-CH_3), 7.59 (q, J = 7.5 Hz, 2-CH_2).

Anal. Calcd for $C_{29}H_{29}N$: C, 89.0; H, 7.5. Found: C, 89.0; H, 7.5.

Addition of 2-Methyl-3,4,5-triphenylcyclopentadienone (31) to Azirines. The general procedure was used and the times for reflux given in the text.

2-Phenyl-1-azirine (2a) and **31** afforded a 2:1 mixture of **32a**: **33a** after 30 hr. Chromatography with benzene eluent afforded 5-methyl-2,3,4,6-tetraphenyl-3*H*-azepine (**33a**) (28%) as bright yellow granules: mp 170° from ethanol; nmr τ 8.2 (5-CH_3), 3.83 (3-H).

Anal. Calcd for $C_{31}H_{25}N$: C, 90.5; H, 6.1. Found: C, 90.2; H, 6.2.

Continued elution using dichloromethane gave 2-methyl-3,4,5,6-tetraphenyl-3*H*-azepine (**32a**) (59%) as pale yellow needles: mp 174° from ethanol; nmr τ 7.81 (d, J = 0.9 Hz, 2-CH_3), 4.36 (3-H).

Anal. Calcd for $C_{31}H_{25}N$: C, 90.5; H, 6.1. Found: C, 90.6; H, 6.0.

3-Methyl-2-phenyl-1-azirine (2b) and **31** gave a 1:1.4 mixture of **32b**:**33b** after 4 days. Chromatography using benzene eluent afforded 5,7-dimethyl-2,3,4,6-tetraphenyl-3*H*-azepine **(33b)** (53%) as lemon yellow crystals from chloroform–ethanol: mp 165°; nmr τ 8.38 (5-CH_3), 8.36 (7-CH_3), 3.94 (3-H).

Anal. Calcd for $C_{32}H_{27}N$: C, 90.3; H, 6.4. Found: C, 90.3; H, 6.5.

Elution with chloroform then gave colorless needles from ethanol of 2,7-dimethyl-3,4,5,6-tetraphenyl-3*H*-azepine **(32b)**: mp 164°; nmr τ 7.8 (2-CH_3), 8.29 (7-CH_3), 4.49 (3-H).

Anal. Calcd for $C_{32}H_{27}N$: C, 90.3; H, 6.4. Found: C, 90.1; H, 6.6.

2,3-Diphenyl-1-azirine (2c) and **31** afforded a 1:6 mixture of **32c**:**33c** after 7 days. Two recrystallizations of the residue from ethanol afforded 5-methyl-2,3,4,6,7-pentaphenyl-3*H*-azepine **(33c)** (51%) as pale yellow crystals: mp 187°; nmr τ 8.32 (5-CH_3), 3.83 (3-H).

Anal. Calcd for $C_{37}H_{29}N$: C, 91.1; H, 6.0. Found: C, 90.8; H, 6.2.

Two recrystallizations of the combined filtrate material afforded 2-methyl-3,4,5,6,7-pentaphenyl-3*H*-azepine **(32c)** (8%) as pale yellow crystals: mp 206°; nmr τ 7.76 (2-CH_3), 4.36 (3-H).

Anal. Calcd for $C_{37}H_{29}N$: C, 91.1; H, 6.0. Found: C, 91.3; H, 6.1.

2-*p*-Methoxyphenyl-1-azirine (2f) (prepared *in situ* from the vinyl azide) and **31** afforded a 5:1 mixture of **32f**:**33f** after 30 hr. Two recrystallizations of the residue from chloroform–ethanol afforded 6-*p*-methoxyphenyl-2-methyl-3,4,5-triphenyl-3*H*-azepine **(32f)** (45%) as pale yellow needles: mp 197°; nmr τ 7.82 (d, J = 0.8 Hz, 2-CH_3), 6.43 (OCH_3), 4.38 (3-H).

Anal. Calcd for $C_{32}H_{27}NO$: C, 87.0; H, 6.2. Found: C, 86.7; H, 6.1.

Preparative layer chromatography (SiO_2, ether–petroleum, 1:2) of the combined filtrate material afforded 6-*p*-methoxyphenyl-5-methyl-2,3,4-triphenyl-3*H*-azepine **(33f)** (9%) as bright yellow needles from chloroform–ethanol: mp 192°; nmr τ 8.2 (5-CH_3), 6.22 (OCH_3), 3.86 (3-H).

Anal. Calcd for $C_{32}H_{27}NO$: C, 87.0; H, 6.2. Found: C, 86.8; H, 6.3.

1,3-Diphenylinden-2-one (16) and Azirines. The dimer of **16** (2 mmol) and the azirine (3 mmol) were heated under reflux in xylene (15 ml). Reaction with azirines **2a** and **2b** required 3 hr, and with azirine **2c** the reaction required 10 hr. The solvent was removed and the residue dissolved in the minimum amount of benzene and then added to a dry column of neutral alumina. Elution with ether–pentane (1:1) directly, afforded the following pure adducts.

3,4,7-Triphenylbenz[*e*]-2*H*-azepine (18a)[43] recrystallized from ethanol as colorless needles (65%): mp 157°; nmr τ 5.06 (d, J = 10 Hz, eq 2-H), 6.4 (d, J = 10 Hz, ax 2-H).

Anal. Calcd for $C_{28}H_{21}N$: C, 90.5; H, 5.7. Found: C, 90.7; H, 5.5.

2-Methyl-3,4,7-triphenylbenz[*e*]-2*H*-azepine (18b) recrystallized from chloroform–ethanol as colorless crystals (68%): mp 201°; nmr τ 8.55 (d, J = 6.5 Hz, 2-CH_3), 6.4 (q, J = 6.5 Hz, 2-H).

Anal. Calcd for $C_{29}H_{23}N$: C, 90.35; H, 6.0. Found: C, 90.3; H, 5.9.

When toluene was used as solvent for the reaction, it required 7 days to reach completion.

2,3,4,7-Tetraphenylbenz[*e*]-2*H*-azepine (18c) recrystallized from chloroform–hexane as pale yellow crystals (63%): mp 185°; nmr τ 5.3 (2-H).

Anal. Calcd for $C_{34}H_{25}N$: C, 91.2; H, 5.6. Found: C, 91.0; H, 5.6.

Phencyclone (17) and azirine cycloadditions were conducted by heating **17** (2.6 mmol) and the azirine (2.8 mmol) in toluene (15 ml) under reflux for 2–3 days. The residue, after removal of the solvent, was dissolved in the minimum volume of chloroform and added to a dry Woelm neutral alumina column. Elution with chloroform afforded the following adducts.

3,4,7-Triphenylphenanthro[9,10-*e*]-2*H*-azepine (19a) crystallized from chloroform–hexane as colorless flocculent crystals (69%): mp 258°; nmr τ 5.09 (d, J = 9 Hz, eq 2-H), 6.4 (d, J = 10 Hz, ax 2-H).

Anal. Calcd for $C_{36}H_{25}N$: C, 91.7; H, 5.3. Found: C, 91.5; H, 5.3.

2-Methyl-3,4,7-triphenylphenanthro[9,10-*e*]-2*H*-azepine (19b) crystallized from chloroform–hexane as colorless flocculent needles (71%): mp 231°; nmr τ 8.55 (d, J = 6.5 Hz, 2-CH_3), 5.91 (q, J = 6.5 Hz, 2-H).

Anal. Calcd for $C_{37}H_{27}N$: C, 91.5; H, 5.60. Found: C, 91.3; H, 5.5.

2,3,4,7-Tetraphenylphenanthro[9,10-*e*]-2*H*-azepine (19c) crystallized from benzene–heptane as pale yellow granules (84%): mp 174°; nmr (C_6D_6) τ 4.57 (2-H).

Anal. Calcd for $C_{42}H_{29}N$: C, 92.1; H, 5.3. Found C, 91.9; H, 5.6.

2,3-Diethyl-4,7-diphenylphenanthro[9,10-*e*]-2*H*-azepine (19d) crystallized from chloroform–ethanol as pale yellow crystals (90%): mp 215°; nmr τ 8.91 (t, J = 7.5 Hz, 3-Et), 8.99 (t, J = 7 Hz, 2-Et), 6.9–8.1 (m, 4), 6.41 (dd, J = 9 and 9 Hz, 2-H).

Anal. Calcd for $C_{34}H_{29}N$: C, 90.4; H, 6.5. Found: C, 90.1; H, 6.6.

Rearrangements of the Phenanthro-2*H*-azepines 19a–d. A general procedure is given for (1) basic and (2) thermal rearrangement.

(1) Basic. The azepine (0.5 mmol) and potassium *tert*-butoxide (0.6 mmol) were heated under reflux in dry dimethoxyethane (5 ml) for 10 hr. The solvent was removed and the residue purified by ptlc on silica.

(2) Thermal. The azepine (0.5 mmol) was either heated neat or in triglyme (5 ml) at *ca.* 200° for 8 hr. Purification was achieved as for (1). The following 3*H*-azepines were obtained using either of these techniques. Yields were 30–90% and chloroform–ethanol was used for recrystallization.

2,5,6-Triphenylphenanthro[9,10-*c*]-3*H*-azepine (20a) crystallized as brilliant yellow crystals: mp 237°; nmr τ 3.67 (3-H).

Anal. Calcd for $C_{36}H_{25}N$: C, 91.7; H, 5.3. Found: C, 91.4; H, 5.6.

7-Methyl-2,5,6-triphenylphenanthro[9,10-*c*]-3*H*-azepine (20b) crystallized as bright yellow crystals: mp 248°; nmr τ 7.87 (2-CH_3), 3.92 (3-H).

Anal. Calcd for $C_{37}H_{27}N$: C, 91.5; H, 5.6. Found: C, 91.4; H, 5.8.

2,5,6,7-Tetraphenylphenanthro[9,10-*c*]-3*H*-azepine (20c) crystallized as pale yellow crystals: mp 264°; nmr τ 3.75 (3-H).

Anal. Calcd for $C_{42}H_{29}N$: C, 92.1; H, 5.3. Found: C, 91.8; H, 5.4.

6,7-Diethyl-2,5-diphenylphenanthro[9,10-*c*]-3*H*-azepine (20d), crystallized as golden needles: mp 211°; nmr τ 8.97 (t, J = 8 Hz, CH_3), 8.85 (t, J = 7 Hz, CH_3).

Anal. Calcd for $C_{34}H_{29}N$: C, 90.4; H, 6.5. Found: C, 90.3; H, 6.6.

1b and 1,2,3-Triphenylcyclopropene (22). The dienone (2.5 g, 9.6 mmol) and the cyclopropene (2.7 g, 10 mmol) were heated under reflux for 4 hr. Removal of the solvent and recrystallization of the residue from chloroform–ethanol afforded colorless needles (4.7 g, 92%) of 1,5-dimethyl-2,3,4,6,7-pentaphenyltricyclo[3.2.1.^{1,5}0.^{2,4}]oct-6-en-8-one **(25)**: mp 202° dec; ν_{max} (KBr) 1760 cm^{-1}; τ ($CDCl_3$) 9.11 (s, 6 H), 7.13 (s, 1 H), 3.80–3.50 (m, 2 H), 3.30–2.70 (m, 23 H).

Anal. Calcd for $C_{40}H_{32}O$: C, 90.9; H, 6.1. Found: C, 91.0; H, 6.0.

Photochemical Decarbonylation of 25. The ketone (1.0 g) was dissolved in dichloromethane (70 ml) and irradiated at 254 nm in a Rayonet photochemical reactor for 4.5 hr. Removal of the solvent gave a colorless solid (0.95 g, 100%). Rapid recrystallization from chloroform–ethanol afforded colorless crystals of 3,6-dimethyl-1,2,4,5,7-pentaphenylcycloheptatriene **(27)**: mp 188–192°; τ ($CDCl_3$) 8.25 (s, 6 H), 5.00 (s, 1 H), 3.55–3.20 (m, 4 H), 3.20–2.90 (m, 6 H), 2.90–2.45 (m, 13 H), 2.45–2.15 (m, 2 H).

Anal. Calcd for $C_{39}H_{22}$: C, 93.6; H, 6.4. Found: C, 93.5; H, 6.5.

Thermolysis of the Symmetrical cycloheptatriene 27. The cycloheptatriene (186 mg) was heated under reflux in tetrachloroethylene (5 ml) and the reaction monitored by nmr spectroscopy. The equilibrium did not change much after 5 hr, consisting of about 75% of **26** and minor isomers. The solvent was removed after 17 hr and the residue recrystallized from chloroform–ethanol to give 2,6-dimethyl-1,3,4,5,7-pentaphenylcycloheptatriene **(26)** as colorless crystals: mp 189°; τ ($CDCl_3$) 8.80 (s, 3 H), 8.15 (s, 3 H), 5.18 (s, 1 H), 3.75–3.45 (m, 2 H), 3.25–2.30 (m, 23 H).

Anal. Calcd for $C_{39}H_{32}$: C, 93.6; H, 6.4. Found: C, 93.3; H, 6.5.

Thermolysis of the Ketone 25. The ketone (180 mg) was heated under reflux in xylene (6 ml) for 20 hr. Removal of the solvent and recrystallization of the residue gave pure **26** (110 mg, 64%): mp 189°.

The Indenone 16 and the Cyclopropene 22. The dienone (500 mg, 1.77 mmol) and the cyclopropene (475 mg, 1.77 mmol) were heated under reflux in toluene (15 ml) for 2 days. The solvent was removed and the nmr spectrum of the residue showed it to be a 4:1 mixture of **30**:**28.** Chromatography on neutral alumina and elution with ether–pentane (1:1) afforded 1,2,3,4,5-pentaphenyl-3*H*-benzocycloheptatriene **(30)** as pale orange needles from chloroform–ethanol: mp 228°; τ ($CDCl_3$) 4.77 (broadish s, 1 H), 3.25–2.20 (m, 29 H).

Anal. Calcd for $C_{41}H_{30}$: C, 94.2; H, 5.8. Found: C, 94.2; H, 5.8.

Elution with ether afforded *exo*-1,2,3,4,5-pentaphenyltricyclo[3.2.1.^{1,5}.0^{2,4}]benzo[*f*]oct-6-en-8-one **(28)** as colorless plates from chloroform–ethanol: mp 249°; ν_{max} (KBr) 1776 cm^{-1}; τ ($CDCl_3$) 6.15 (s, 1 H), 3.55–2.15 (m, 29 H).

Anal. Calcd for $C_{42}H_{30}O$: C, 91.6; H, 5.5. Found: C, 91.5; H, 5.4.

Phencyclone (17) and Cyclopropene 22. The dienone (1.0 g, 2.62 mmol) and the cyclopropene (0.75 g, 2.8 mmol) were heated under reflux in toluene (15 ml) for 10 hr. The mixture was allowed to cool and the solid (1.1 g) filtered off. Fractional recrystallization from chloroform afforded first 1,2,3,4,5-pentaphenylphenanthro[9,10-*g*]-3*H*-cycloheptatriene **(23)** as colorless crystals: mp 319°.

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Anal. Calcd for $C_{49}H_{34}$: C, 94.5; H, 5.5. Found: C, 93.1; H, 5.4.

Secondly, *exo*-1,2,3,4,5-pentaphenylphenanthro[9,10-*f*]tricyclo-[3.2.1^{1,5}.0^{2,4}]oct-6-en-8-one (**29**) crystallized as colorless needles: mp 270°; ν_{max} (KBr) 1776 cm^{-1}.

Anal. Calcd for $C_{50}H_{34}O$: C, 92.3; H, 5.3. Found: C, 91.1; H, 5.2.

Registry No.—**1a,** 479,33-4; **1b,** 26307-17-5; **1c,** 51932-77-5; **2a,** 7654-06-0; **2b,** 16205-14-4; **2c,** 16483-98-0; **2d,** 52124-00-2; **2e,** 18709-44-9; **2f,** 32687-32-4; **3a,** 33070-61-0; **3b,** 33070-63-2; **3c,** 33070-66-5; **3d,** 52124-01-3; **3e,** 33654-83-0; **3f,** 33070-60-9; **3g,** 33070-62-1; **3h,** 33070-65-4; **3i,** 52124-02-4; **3j** picrate, 51932-79-7; **3k,** 52124-03-5; **4a,** 52124-04-6; **5b,** 52124-05-7; **10,** 18709-43-8; **11,** 33654-82-9; **12,** 33654-81-8; **16,** 23414-46-2; **17,** 5660-91-3; **18a,** 39934-14-0; **18b,** 39934-15-1; **18c,** 39934-16-2; **19a,** 39934-03-7; **19b,** 39934-04-8; **19c,** 52124-06-8; **19d,** 52124-07-9; **20a,** 52124-08-0; **20b,** 52124-09-1; **20c,** 52124-10-4; **20d,** 52124-11-5; **22,** 16510-49-9; **23,** 52124-12-6; **25,** 52154-42-4; **26,** 52124-13-7; **27,** 52124-14-8; **28,** 52154-43-5; **29,** 52124-15-9; **30,** 39934-07-1; **31,** 33535-80-7; **32a,** 52124-16-0; **32b,** 52124-17-1; **32c,** 52124-18-2; **32f,** 52124-19-3; **33a,** 52124-20-6; **33b,** 52124-21-7; **33c,** 52124-22-8; **33f,** 52124-23-9.

References and Notes

(1) Cycloadditions. XVII. For the previous paper in the series see ref 9b.
(2) For preliminary communications see (a) D. J. Anderson and A. Hassner, *J. Amer. Chem. Soc.*, **93,** 4339 (1971); (b) A. Hassner and D. J. Anderson, *ibid.*, **94,** 8255 (1972).
(3) (a) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, **90,** 2869 (1968); (b) for a review on azirines, see F. W. Fowler in "Advances in Heterocyclic Chemistry," Vol. 13, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1971, p 45.
(4) A. Hassner, A. S. Miller, and M. J. Haddadin, *Tetrahedron Lett.*, 1353 (1972).
(5) F. P. Woerner, H. Reimlinger, and R. Merenyi, *Chem. Ber.*, **104,** 2786 (1971).
(6) V. Nair, *Tetrahedron Lett.*, 4831 (1971).
(7) V. Nair, *J. Org. Chem.*, **37,** 802 (1972).
(8) H. Hemetsberger and D. Knittel, *Monatsh. Chem.*, **103,** 205 (1972).
(9) (a) V. Nair, *J. Org. Chem.*, **37,** 2508 (1972); (b) A. Hassner and D. J. Anderson, *ibid.*, **39,** 2031 (1974).
(10) V. Nair, *J. Org. Chem.*, **33,** 2121 (1968).
(11) A. Padwa, S. Clough, M. Dhara, J. Smolanoff, and S. I. Wetmore, *J. Amer. Chem. Soc.*, **94,** 1395 (1972).
(12) A. Padwa, J. Smolanoff, and S. I. Wetmore, *J. Chem. Soc., Chem. Commun.*: (a) 404 (1972); (b) 1116 (1972).
(13) N. Gakis, M. Maerky, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55,** 748 (1972).
(14) A. Padwa and J. Smolanoff, *J. Amer. Chem. Soc.*, **93,** 549 (1971).
(15) A. Padwa, D. Dean, and J. Smolanoff, *Tetrahedron Lett.*, 4087 (1972).
(16) H. Giezendanner, M. Maerky, B. Jackson, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55,** 745 (1972).
(17) For a review on azepines see L. A. Paquette in "Nonbenzenoid Aromatics," Vol. I, J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, p 249.
(18) R. J. Sundberg, S. R. Suter, and M. Brenner, *J. Amer. Chem. Soc.*, **94,** 513 (1972).
(19) M. Anderson and A. W. Johnson, *J. Chem. Soc. C*, 2411 (1965).
(20) W. Dittmar, J. Sauer, and A. Steigel, *Tetrahedron Lett.*, 5171 (1969).
(21) E. Cartensen-Oeser, *Chem. Ber.*, **105,** 982 (1972).
(22) A. Steigel, J. Sauer, D. A. Kleier, and G. Binsch, *J. Amer. Chem. Soc.*, **94,** 2770 (1972).
(23) M. J. S. Dewar and N. Trinajstic, *Tetrahedron*, **26,** 4269 (1970).
(24) S. Sternhell, *Quart. Rev.*, **23,** 236 (1969).
(25) M. D. Mehta, D. Miller, and E. F. Mooney, *J. Chem. Soc.*, 6695 (1965).
(26) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89,** 2077 (1967).
(27) A. Hassner and F. W. Fowler *J. Amer. Chem. Soc.*, **90,** 2869 (1968).
(28) This is in contrast to the reaction of azirine with cyclopropenones, A. Hassner and A. Kascheres, *J. Org. Chem.*, **37,** 2328 (1972), where the C–N bond of the azirine is broken.
(29) Although 3,3-dimethylcyclopropene failed to react with cyclopentadiene [G. L. Closs, L. E. Closs, and W. A. Boll, *J. Amer. Chem. Soc.*, **86,** 3796 (963)], it did react with 3,6-diphenyl-5-tetrazine.[22]
(30) The sluggishness of 3-carbomethoxycyclopropenes in Diels–Alder additions has already been noted: (a) M. A. Battiste, *Tetrahedron Lett.*, 3795 (1964); (b) M. A. Battiste and T. J. Barton, *ibid.*, 1227 (1967).
(31) S. C. Clarke and B. L. Johnson, *Tetrahedron*, **27,** 3557 (1971).
(32) W. Dilthey, I. ter Horst, and W. Schommer, *J. Prakt. Chem.*, **143** 189 (1935).
(33) The reaction of **16** with azirines was somewhat sluggish in refluxing toluene probably due to the slow dissociation of the dimer at this temperature.
(34) M. A. Battiste, *J. Amer. Chem. Soc.*, **85,** 2175 (1963).
(35) B. Halton, M. A. Battiste, R. Rehberg, C. L. Deyrup, and M. E. Brennan, *J. Amer. Chem. Soc.*, **89,** 5964 (1967).
(36) E. L. Allred and A. L. Johnson, *J. Amer. Chem. Soc.*, **93,** 1300 (1971), and references therein.
(37) Varian Index No. 318.
(38) H. Newman and R. B. Angier, *Tetrahedron*, **26,** 825 (1970).
(39) L. A. Paquette, *J. Amer. Chem. Soc.*, **86,** 4096 (1964).
(40) T. J. van Bergen and R. M. Kellogg, *J. Org. Chem.*, **36,** 978 (1971).
(41) A. Mannschreck, G. Rissmann, F. Vogtle, and D. Wild, *Chem. Ber.*, **100,** 335 (1967).
(42) All melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 457 spectrophotometer as KBr pellets Nmr spectra were recorded with a Varian A-60A spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as a solvent. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.
(43) Since the numbering of the azepine system is not completely systematic,[17] the lettering system adopted in this paper follows the numbers

3*H*

2*H*

Reactions of 3*H*-Azepines Derived from Cyclopentadienones and 1-Azirines[1]

David J. Anderson, Alfred Hassner,* and David Y. Tang

Chemistry Department, University of Colorado, Boulder, Colorado 80302

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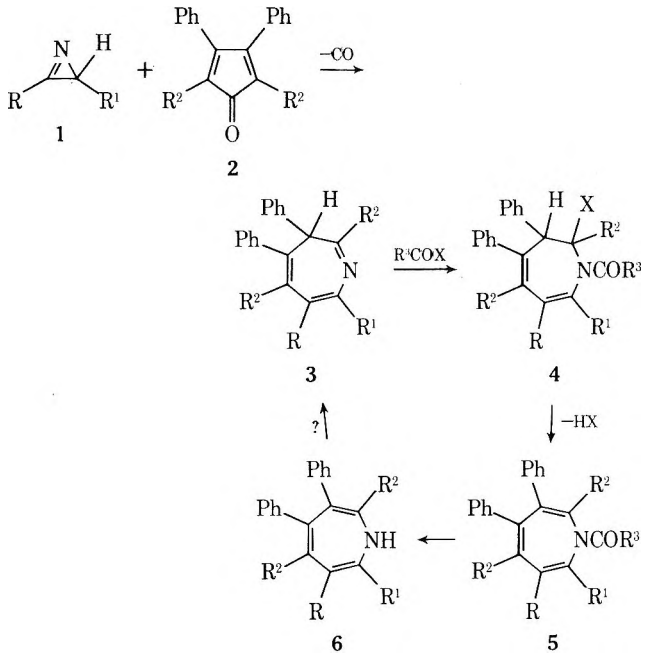
Reactions of 3*H*-azepines **3,** available from cycloaddition of 1-azirines with cyclopentadienones, were examined with a view to producing 1*H*-azepine derivatives. Treatment of **3** with benzoyl chloride resulted in 2-alkylidine-*N*-benzoyl- 2,3-dihydro-1-azepines (**7**), which failed to isomerize to the antiaromatic system **5.** Photolysis of **7** led to 1,3 (N to C) benzoyl transfer. Attempted base-catalyzed deuterium exchange underlined the difficulty of isolating an 8-π-electron system. Acid isomerization of 7-unsubstituted azepines **3a–c** produced substituted anilines, presumably *via* unstable 1-azepines, while the 7-methyl substrate **19** afforded cyclohexadienone products.

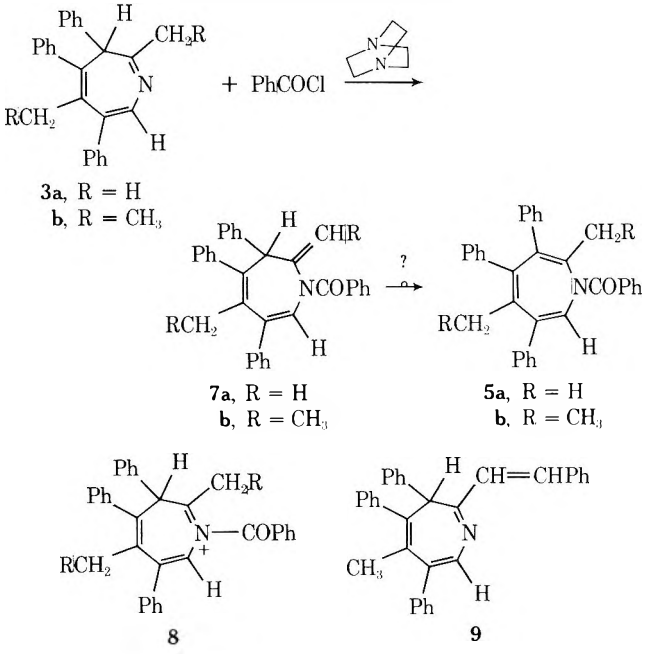
Recently we have developed[1,2] a procedure for the preparation of 3*H*-azepines **3** by cycloaddition of 1-azirines **1** with cyclopentadienones **2.** Such compounds might provide an entry into the interesting 8-π-electron system,[3] the 1*H*-azepine **5** or **6.** For instance, addition of acid chlorides to the imine double bond of **3** may lead directly or *via* **4** to the N-substituted 1*H*-azepine **5.** Removal of RCO from **5** could give the elusive N-unsubstituted 1*H*-azepine **6,** which in our case should be stabilized by the multiple substitution on the ring carbons. Alternatively, **6** might just revert to **3,** since it has been shown that the 3*H*-azepine is in general the thermodynamically more stable isomer.



Results and Discussion

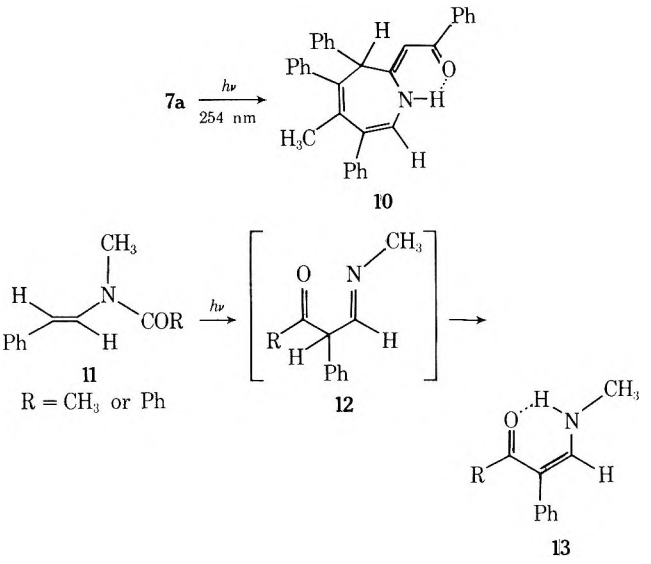
Addition of benzoyl chloride to the azepine **3a** in benzene proceeded fairly rapidly to give a new product. The formation of this product was enhanced by the presence of 1,4-diazabicyclo[2.2.2]octane (Dabco) in the solution. Mass spectral and elemental analyses showed it to be an HCl elimination product of an azepine–benzoyl chloride adduct. Infrared showed an amide absorption at 1640 cm^{-1} while nmr demonstrated the loss of one methyl group with the concurrent appearance of a methylene (=CH_2) group at *ca.* 5.0 ppm. These data suggested the *exo*-methylene structure **7a**. The ethylidene derivative **7b** likewise showed nmr absorptions consistent with its structure.

The reaction may involve formation of intermediate **8**, or benzoylation of the enamine tautomer of the imine **3**. Evidence supporting this pathway was found in the easy exchange of the protons of the 2-methyl group in **3a** with D_2O in analogy with the D exchange reported for **19**.[5] The acidity of these protons is also apparent from the ease of formation of the benzylidene derivative **9** from **3a** with benzaldehyde.[5,6] When the 2-methyl group of **3** was replaced by a phenyl group as in **3c**, there was no reaction with benzoyl chloride even under forcing conditions.

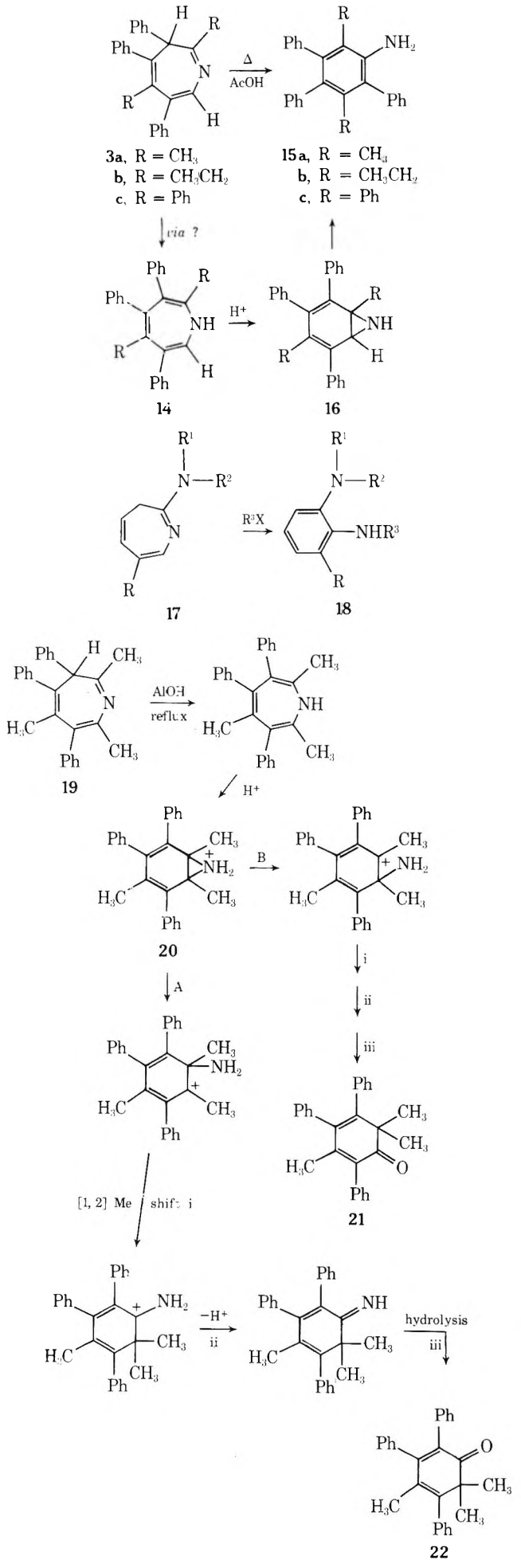


Several attempts were made to isomerize the *exo*-methylene azepine **7a** to the conjugated 1*H* isomer **5a**. With various bases, either no reaction took place (weak bases) or simple debenzoylation took place (strong bases, *e.g.*, KO-*t*-Bu) to regenerate **3a**. No exchange of the benzylic 3 proton in **3a** was observed even in the presence of potassium *tert*-butoxide in *t*-BuOD, in spite of the fact that the 2-methyl protons readily exchanged.[7] This differential behavior of the endocyclic *vs.* the exocyclic protons α to the C=N in **3** and the failure to achieve isomerization to **5** may be indicative of the low stability inherent in the anti aromatic 8-π-electron 1*H*-azepines.

Attempted photochemical transformation of **7a** to **5** resulted only in a benzoyl transfer to give the amino ketone **10**. The strong H bonding of the NH to the C=O was evident by the low-field (τ − 3.05) appearance of the NH. Additional structure proof came from the fact that the NH and the vinylic azepine ring proton were coupled (J = 5 Hz). This coupling disappeared on exchange with D_2O. This type of transformation, which corresponds to a nonaromatic photo-Fries rearrangement,[8a] has also been observed in the photolysis of **11** to **13**, presumably *via* **12**. The proposed mechanism may involve a radical pair.[8b]

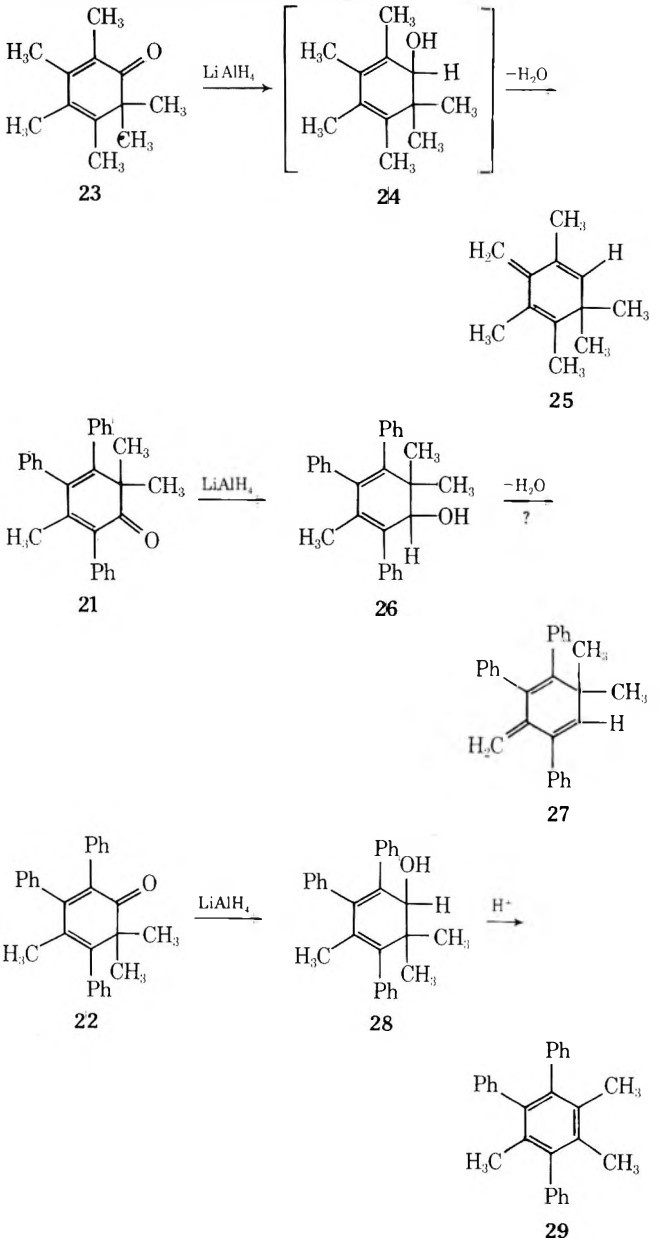


When acetic acid was used as an isomerization catalyst on **7a**, minute quantities of aniline derivatives were detected together with much polymeric and resinous material. Investigation of the reaction of 3*H*-azepine **3a** with glacial acetic acid revealed that a very clean and efficient isomerization to **15a** took place within 2 hr at reflux temperature. No side products were detected. The presence of an $-NH_2$ group in **15a** was clear from both the nmr and ir spectra. An equally facile reaction was observed with the diethyl-3*H*-azepine **3b**. The isomerization of the pentaphenyl-3*H*-azepine **3c** required a reflux time of 4 days to achieve complete conversion to pentaphenylaniline **15c**. The reaction may be interpreted as involving isomerization of the 3*H*-azepine to its 1*H* isomer **14**, which then undergoes ring contraction[9] to the azanorcaradiene **16** in acid, to give finally the aniline **15**. N-Substituted 1*H*-azepines have been found[10] to rearrange to anilines in the presence of acid. Not too dissimilar ring contractions have been reported[11] for other 3*H*-azepines (*i.e.*, **17** → **18**). The important criterion for our observed 3*H*-azepine → aniline conversions was the presence of the ring proton at the 7 position of the azepine nucleus. When this was replaced by a CH_3 group as in **19**, the reaction took a different course inasmuch as the mix-



ture became dark brown and very complex (by tlc). However one homogeneous product was isolated (mp 198°) possessing the following spectral properties: mol wt 364, empirical formula $C_{27}H_{24}O$ (364) by elemental analysis, ν_{max} 1656 cm^{-1}. The nmr spectrum was quite unusual, since besides 15 aromatic protons, there was a nine-proton singlet at τ 8.66 in $CDCl_3$. The nine-proton signal appeared as a narrowly spaced doublet in C_6D_6, but addition of $Eu(fod)_3$ caused the doublet to separate into a three-proton singlet and a six-proton singlet. The six-proton singlet experienced the greatest downfield shift upon addition of increasing amounts of $Eu(fod)_3$. The ir absorption at 1656 cm^{-1} is consistent with an $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl, and the nmr suggested a *gem*-dimethyl group in closer proximity to the carbonyl than the other lone methyl group [$Eu(fod)_3$ shifts].

Consideration of a possible mechanistic pathway and of the spectral data suggests structures **21** or **22**. Formation of the protonated azanorcaradiene **20** may be postulated in analogy to **3** → **14** → **16** → **15**. **20** can then open by either pathway A or pathway B, both of which involve a [1,2]-methyl shift followed by deprotonation and hydrolysis. In order to distinguish between regioisomers **21** and **22** we compared the $LiAlH_4$ reduction product with that[12] from hexamethylcyclohexadienone **23** (ν_{max} 1647 cm^{-1}). In the



latter the intermediate allylic alcohol was exceedingly unstable and readily underwent a 1,4-elimination of H_2O to give the hydrocarbon **25**. We could reasonably expect that if our isolated ketone had structure **21**, than a similar reduction might lead to the hydrocarbon **27** *via* the allylic alcohol **26**. On the other hand reduction of **22** should lead to the alcohol **28** with little tendency to eliminate H_2O.

Reduction with $LiAlH_4$ of the dienone, followed by an acidic work-up, gave an alcohol stable to dilute HCl and assigned structure **28**. This was further confirmed by the dehydration–rearrangement of **28** to **29** in acetic acid–sulfuric acid. As expected, the methyl protons between the two phenyl groups are shielded (τ 8.28)[13] compared with the other two methyl groups (τ 7.98). Consequently we have assigned the cyclohexadienone structure **22** to the product isolated from 3*H*-azepine **19** and acetic acid. It is possible that **21** may also be present in the reaction mixture but that, owing to the complex nature of the reaction, it was not isolated.

Experimental Section

Reaction of 2,5-Dimethyl-3,4,6-triphenyl-3*H*-azepine (3a) with Benzoyl Chloride in the Presence of Dabco. The azepine[2] (5.0 g, 14.3 mmol) was dissolved in benzene (50 ml) and Dabco (1.65 g, 14.7 mmol) was added. The mixture was stirred at 25° and benzoyl chloride (2.5 g, 17.7 mmol) dissolved in benzene (10 ml) was added dropwise. The mixture was stirred overnight and then poured into water (400 ml). The organic layer was separated and dried ($MgSO_4$). Removal of the solvent gave a pale yellow solid. Recrystallization from hexane gave pale yellow plates (5.4 g, 83%) of 1-benzoyl-1*H*-5-methyl-2-methylene-3,4,6-tripheny l-3*H*-azepine (**7a**): mp 160°; nmr ($CDCl_3$) τ 8.38 (s, CH_3), 5.06 (br s, =CHH), 4.97 (br s, =CHH), 4.76 (s, CH), 3.73 (s, =CH), 3.10–2.30 (m, 20 H); ν_{max} (KBr) 1690, 1640, 1597, 1325, 1250, 870, and 695 cm^{-1}; mass spectrum *m/e* 453, 377, 362, 349, 348, 334, 308, 258, 257, 215, 105, 91, 78, 77.

Anal. Calcd for $C_{33}H_{21}NO$: C, 87.4; H, 6.0. Found: C, 87.5; H, 6.1.

Reaction of Phenylazirine with 2,5-Diethyl-3,4-diphenylcyclopenta-2,4-dienone. α-Styryl azide (1.45 g, 10 mmol) was heated under reflux in toluene (25 ml) for 2 hr. The dienone (2.3 g, 8 mmol) was then added and the mixture was refluxed for 17 hr. Removal of the solvent gave a reddish oil. Purification was achieved by chromatography over alumina to afford **2,5-diethyl-3,4,6-triphenyl-3*H*-azepine (3b)** as a colorless oil (3.0 g, 99%): nmr ($CDCl_3$) τ 9.28 (t, J = 7.5 Hz, 3 H), 8.05–7.25 (m, 4 H), 4.70 (s, 1 H), 3.00–2.40 (m, 16 H) (possible 1 H singlet at τ 2.85). The picrate was obtained as yellow microneedles from ethanol, mp 169°.

Anal. Calcd for $C_{34}H_{30}N_4O_7$: C, 67.3; H, 5.0; N, 9.2. Found: C, 67.3; H, 5.0; N, 9.2.

Reaction of the Diethyl-3*H*-azepine 3b with Benzoyl Chloride in the Presence of Dabco. The azepine (400 mg, 1.06 mmol) was dissolved in benzene (25 ml) and Dabco (120 mg, 1.07 mmol) was added. Benzoyl chloride (160 mg, 1.14 mmol) was added and the mixture was heated under reflux for 6 hr. After cooling, the mixture was poured into water (50 ml) and the bright yellow benzene layer was separated and dried ($MgSO_4$). Removal of the solvent gave a yellow-brown oil (450 mg) which crystallized on prolonged trituration. Recrystallization from hexane gave 1-benzoyl-1*H*-2-ethylidene-5-ethyl-3,4,6-triphenyl-3*H*-azepine (**7b**) as bright yellow crystals: mp 68°; nmr ($CDCl_3$) τ 9.25 (t, J = 7.5 Hz, CH_3CH_2), 8.47 (d, J = 7.25 Hz, CH_3CH), 8.22–7.62 (m, CH_3CH_2), 4.63 (br s, CH), 4.32 (q, J = 7.25 Hz, $CHCH_3$), 3.56 (s, =CH), 3.10–2.20 (m, 20 H); ν_{max} (KBr) 1682, 1594, 1276, 1245, 895, and 707 cm^{-1}.

Anal. Calcd for $C_{35}H_{31}NO$: C, 87.3; H, 6.5; N, 2.9. Found: C, 87.4; H, 6.6; N, 3.0.

Photolysis of the *exo*-Methylene Azepine 7a. The azepine (500 mg, 1.1 mmol) was dissolved with difficulty in dioxane (50 ml) in a quartz vessel and irradiated at 254 nm in a Rayonet reactor. After 60 hr the solvent was removed to give a brown oil. Chromatography (neutral Al_2O_3) with graduate elution from hexane to methylene chloride afforded the major fraction in the more polar fractions. Recrystallization from chloroform–hexane gave dark yellow crystals (145 mg, 29%) of the amino ketone **10**: mp 201–205°; nmr ($CDCl_3$) τ 8.35 (s, 3 H), 5.17 (br s, 1 H), 4.14 (s, 1 H), 3.73 (d, J = 5 Hz, 1 H), 3.10–2.40 (m, 18 H), 2.20–1.95 (m, 2 H), −3.05 (v br d, J = 5 Hz, 1 H) (addition of D_2O caused the τ −3.05 signal to disappear and the doublet at τ 3.73 to collapse to a singlet); ν_{max} (KBr) 1560 (vs), 1423, 1395, 1374, 760, and 709 cm^{-1}; mass spectrum *m/e* 453, 436, 376, 348, 337, 308, 270, 215.

Anal. Calcd for $C_{33}H_{27}NO$: C, 87.4; H, 6.0. Found: C, 87.4; H, 6.0.

Reaction of 2,5-Dimethyl-3,4,6-triphenyl-3*H*-azepine (3a) with Acetic Acid. The azepine (200 mg, 0.575 mmol) was heated under reflux in glacial acetic acid (5 ml) for 2 hr. Removal of the solvent gave a buff-colored solid (140 mg, 70%). Recrystallization from ethanol gave pale yellow plates of **2,5-dimethyl-3,4,6-triphenylaniline (15a)**: mp 241°; nmr ($CDCl_3$) τ 8.26 (s, 3 H), 8.07 (s, 3 H), 6.12 (br s, 2 H, NH_2), 3.20–2.80 (m, 10 H), 2.70–2.40 (m, 5 H); ν_{max} (KBr) 3460, 3380, 1607, 750, and 701 cm^{-1}; mass spectrum *m/e* 349 (100%), 333, 261, 215.

Anal. Calcd for $C_{26}H_{23}N$: C, 89.5; H, 6.6. Found: C, 89.2; H, 6.5.

Reaction of 2,5-Diethyl-3,4,6-triphenyl-3*H*-azepine (3b) with Acetic Acid. The azepine (450 mg, 1.19 mmol) was heated under reflux in glacial acetic acid (5 ml) for 2.5 hr. Removal of the solvent and passage of the residue in ether through a short, dry packed column of Merck alumina gave an orange oil which rapidly solidified. Recrystallization from chloroform–ethanol gave pale orange flakes of **2,5-diethyl-3,4,6-triphenylaniline (15b)**: mp 191°; nmr ($CDCl_3$) τ 9.35 (t, J = 7.5 Hz, 3 H), 8.97 (t, J = 7.5 Hz, 3 H), 7.80 (q, J = 7.5 Hz, 2 H), 7.64 (q, J = 7.5 Hz, 2 H), 6.50 (br s, 2 H, NH_2), 2.90 (s, 5 H), 2.88 (s, 5 H), 2.50 (s, 5 H); ν_{max} (KBr) 3465, 3380, 1602, 1421, 754, and 710 cm^{-1}.

Anal. Calcd for $C_{28}H_{27}N$: C, 89.1; H, 7.2. Found: C, 88.9; H, 7.3.

Reaction of 2,3,4,5,6-Pentaphenyl-3*H*-azepine (14) with Acetic Acid. The azepine[2] (226 mg, 0.48 mmol) and acetic acid (8 ml) were heated under reflux for 4 days, after which time solid began to precipitate out of solution. Removal of the solvent and washing of the residue with ether gave a pinkish solid (168 mg, 75%) which was recrystallized from chloroform–ethanol to give colorless crystals of **pentaphenylaniline (15c)**: mp 263–265°; nmr ($CDCl_3$) τ 6.85–6.30 (br, 2 H, NH_2), 3.22 (s, 5 H), 3.17 (s, 10 H), 2.82 (s, 10 H); ν_{max} (KBr) 3465, 3375, 1598, 1410, 750, and 704 cm^{-1}; mass spectrum *m/e* 473, 395, and 378.

Anal. Calcd for $C_{36}H_{27}N$: C, 91.3; H, 5.75. Found: C, 91.3; H, 5.85.

Reaction of 2,5,7-Trimethyl-3,4,6-triphenyl-3*H*-azepine (19) with Acetic Acid. The azepine[2] (3.63 g, 10 mmol) was heated under reflux in glacial acetic acid (30 ml) for 4 hr, during which time the mixture turned dark brown. Removal of the solvent gave a brown oil which was dissolved in chloroform (150 ml) and washed with Na_2CO_3 solution. After drying ($MgSO_4$), the solvent was removed to give a brown, frothy oil (3.6 g). Trituration with ether–pentane gave a yellow solid (1.1 g). Chromatography (Al_2O_3) of the residue did not yield any homogenous fractions. Two recrystallizations of the solid gave very fine, pale yellow needles (436 mg, 12%) of **4,6,6-trimethyl-2,3,5-triphenylcyclohexa-2,4-dienone (22)**: mp 198°; nmr ($CDCl_3$) τ 8.66 (s, 9 H), 3.10–2.50 (m, 15 H); ν_{max} (KBr) 1656, 1335, 1127, 750, 741, and 700 cm^{-1}; mass spectrum *m/e* 364, 349, 336, 321, 306, 291, 243, 229, and 228.

Anal. Calcd for $C_{27}H_{24}O$: C, 89.0; H, 6.6. Found: C, 89.2; H, 6.5.

Reduction of the Cyclohexadienone 22 with $LiAlH_4$. The dienone (200 mg, 0.55 mmol) in anhydrous ether (10 ml) was treated with $LiAlH_4$ (25 mg, 0.66 mmol). The mixture was stirred at 25° for 2 hr and then dilute HCl (15 ml) was added dropwise. Extraction of the organic layer and drying over $MgSO_4$ gave a colorless foam after removal of the solvent. The foam crystallized on trituration with pentane to give a colorless solid (147 mg, 73%). Recrystallization from hexane gave colorless crystals of **4,6,6-trimethyl-2,3,5-triphenylcyclohexa-2,4-dienol(28)**: mp 137°; nmr ($CDCl_3$) τ 9.00 (s, 3 H), 8.70 (s, 6 H), 7.98 (br s, OH), 6.00 (s, 1 H), 3.00–2.50 (m, 15 H); ν_{max} (KBr) 3550, 3450, 767, and 709 cm^{-1}.

Anal. Calcd for $C_{27}H_{26}O$: C, 88.5; H, 7.15. Found: C, 88.4; H, 6.9.

Rearrangement of 28 to 29. To 2 ml of glacial acetic acid was added 21 mg of **28** and 1 drop of concentrated sulfuric acid. The mixture was stirred for 24 hr at room temperature, 10 ml of $CHCl_3$ was added, and the mixture was neutralized to pH 8 with 10% K_2CO_3. The organic layer was dried (Na_2SO_4), the solvent was evaporated to dryness, and the residue (18 mg) was recrystallized from $CHCl_3$–pentane to afford 13.5 mg (66%) of **28** as a white solid, mp 224–226° (lit. mp 223°).[13]

Deuterium Exchange Studies. A solution of **3a** or **3b** (100 mg) in 1 ml of $CDCl_3$ was shaken with 2 drops of D_2O (99.8% d_2) at room temperature and let stand for 1 hr. Nmr indicated a 70% diminution of the CH_3 (or CH_2, respectively) absorption at τ 7.7 with no change in the intensity of the singlet near τ 4.7. Similar re-

sults were found in the presence of potassium tert-butoxide in *tert*-butyl alcohol or if **3a** was stirred in dioxane–D_2O (30:1) at 82° for 24 hr.

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Registry No.—**1** (R = Ph; R^1 = H), 7654-06-0; **2b**, 51932-77-5; **3a**, 33070-60-9; **3b**, 51932-78-6; **3b** picrate, 51932-79-7; **7a**, 51932-80-0; **7b**, 51932-81-1; **10**, 51932-82-2; **14**, 33070-61-0; **15a**, 51932-83-3; **15b**, 51932-84-4; **15c**, 51932-85-5; **19**, 33070-62-1; **22**, 51932-86-6; **28**, 51932-87-7; benzoyl chloride, 98-88-4; acetic acid, 64-19-7.

References and Notes

(1) Cycloadditions. XVIII. For previous paper in the series see A. Hassner and D. J. Anderson, *J. Org. Chem.*, **39**, 3070 (1974).
(2) D. J. Anderson and A. Hassner, *J. Amer. Chem. Soc.*, **93**, 4339 (1971); A. Hassner and D. J. Anderson, *ibid.*, **94**, 8255 (1972).
(3) L. A. Paquette, *Angew. Chem., Int. Ed. Engl.*, **10**, 11 (1971).
(4) G. Schaden, *Chem. Ber.*, **106**, 2084 (1973); R. J. Sundberg, S. R. Suter, and M. Breamer, *J. Amer. Chem. Soc.*, **94**, 513 (1972).
(5) V. Nair, *J. Org. Chem.*, **37**, 802 (1972).
(6) T. J. van Bergen and R. M. Kellogg, *J. Org. Chem.*, **36**, 978 (1971).
(7) At 80° **19** was found (ref 5) to undergo D exchange not only at the C-2 methyl but also at the C-7 methyl function. We found that heating of **3a** at 80° in dioxane–D_2O for 24 hr showed exchange of the C-2 methyl hydrogens but not of the C-7 proton.
(8) (a) D. Bellus, *Advan. Photochem.*, **8**, 109 (1971); (b) R. W. Hoffman and K. R. Eicken, *Chem. Ber.*, **102**, 2987 (1969).
(9) W. D. Stohrer and R. Hoffmann, *Angew Chem., Int. Ed. Engl.*, **11**, 825 (1972).
(10) L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *J. Org. Chem.*, **34**, 2879 (1969).
(11) (a) W. von E. Doering and R. A. Odum, *Tetrahedron Lett.*, 81 (1966); (b) F. R. Atherton and R. W. Lambert, *J. Chem. Soc., Perkin Trans. 1*, 1079 (1973); (c) R. K. Smalley, W. A. Strachan, and H. Suschitzky, *Tetrahedron Lett.*, 825 (1974).
(12) A. J. Waring and H. Hart, *J. Amer. Chem. Soc.*, **86**, 1454 (1964).
(13) H. Dietle and P. M. Maitlis, *Chem. Commun.*, 481 (1968). The originally reported value of τ 7.23 for one of the methyl groups in **29** has been corrected to 8.33 (in CH_2Cl_2): H. Dietle, H. Reinbeiruer, J. Moffat, and P. M. Maitlis, *J. Amer. Chem. Soc.*, **92**, 2276 (1970).

Formation of 5-Aryl-5,6-dihydro-4*H*-1,2,4-thiadiazine 1,1-Dioxides and *N*-*trans*-Styrylamidines by Base Treatment of *N*-(*trans*-Styrylsulfonyl) amidines[1]

W. L. Matier* and W. T. Comer

Department of Chemical Research, Mead Johnson Research Center, Evansville, Indiana 47721

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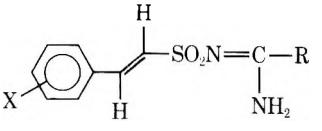
Treatment of *N*-(*trans*-styrylsulfonyl)amidines (**1**) with base affords 5-aryl-5,6-dihydro-4*H*-1,2,4-thiadiazine 1,1-dioxides (**2**) and/or *N*-(*trans*-styryl)amidines (**3**). Formation of **3** is favored by electron-withdrawing substituents in the styryl aromatic ring and by polar reaction solvents. Possible mechanisms for the formation of **2** and **3** are discussed. With electron-rich aromatic rings, intramolecular Michael addition occurs predominantly at the carbon atom β to the sulfonyl group to afford the expected product **2**. However, with electron-withdrawing substituents in the aromatic ring, we propose that addition occurs α to the sulfonyl group to afford an unstable thiadiazoline intermediate, which gives **3** by loss of SO_2. This rearrangement of **1** to **3** is analogous to a Smiles rearrangement in which intramolecular nucleophilic attack occurs on a vinylic rather than an aromatic carbon.

We recently reported the synthesis of 5-aryl-4*H*-1,2,4-thiadiazine 1,1-dioxides by base-catalyzed, intramolecular cyclization of *N*-(α-bromostyrylsulfonyl)amidines.[2] As an approach to the synthesis of 5-aryl-5,6-dihydro-4*H*-1,2,4-thiadiazine 1,1-dioxides (**2**), we treated *N*-(*trans*-styrylsulfonyl)amidines (**1**) with base and obtained dihydrothiadiazines **2** and/or *N*-(*trans*-styryl)amidines **3**. This paper examines some of the parameters which determine the types

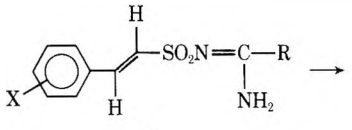
Table I
***N*-(*trans*-Styrylsulfonyl)amidines (1)[a]**



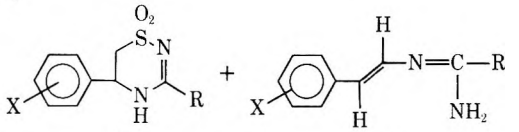
Compd	X	R	Mp, °C	Crystn solvent	Yield, %	Formula
1a	H	Me	134.5–137	*i*-PrOAc	76	$C_{10}H_{12}N_2O_2S$
1b	H	Ph	192.5–194.5	Me_2CO	90	$C_{15}H_{14}N_2O_2S$
1c	4-Cl	Me	166.5–169.5	EtOAc	93	$C_{10}H_{11}ClN_2O_2S$
1d	3,4-Cl_2	Me	197.5–198.5	Me_2CO–*i*-Pr_2O	83	$C_{10}H_{10}Cl_2N_2O_2S$
1e	3,4-Cl_2	Ph	147–150	MeOH	88	$C_{15}H_{12}Cl_2N_2O_2S$
1f	3,4-Cl_2	$PhCH_2$	159–161	*i*-PrOH	81	$C_{16}H_{14}Cl_2N_2O_2S$
1g	4-NO_2	Me	203–203.5	MeCN	92	$C_{10}H_{11}N_3O_4S$
1h	4-NO_2	Ph	171–173	*i*-PrOH	87	$C_{15}H_{13}N_3O_4S$
1i	2-NO_2	Me	175–178	Me_2CO–*i*-Pr_2O	85	$C_{10}H_{11}N_3O_4S$

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for compounds **1a–i**, **2a–f**, and **3a–j**: Ed.

Table II



1



2 3

	X	R	Solvent	2 yield, %	3 yield, %
a	H	Me	DMSO	60	3
b	H	Ph	DMSO	84	6.5
c	4-Cl	Me	DMSO	27	12
d	3,4-Cl_2	Me	DMSO	2	70
e	3,4-Cl_2	Ph	DMSO	3[a]	68[a,b]
f	3,4-Cl_2	$PhCH_2$	DMSO	3	41
f	3,4-Cl_2	$PhCH_2$	Me_2CO	31[c]	
g	4-NO_2	Me	DMSO		46
h	4-NO_2	Ph	Me_2CO		96
i	2-NO_2	Me	Me_2CO		88
j	2-NO_2	Ph	Me_2CO		78[d]

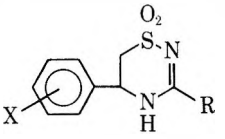
[a] Unreacted starting material was recovered (18%). [b] Compound **3e** was obtained in 49% yield after 30 hr reaction time. [c] Reaction time was 24 hr. [d] Overall yield from 2-nitrostyrylsulfonyl chloride. The intermediate **1j** was not isolated.

cm^{-1}, assigned to NH_2-deformation modes, and C=N absorption at 1520–1560 cm^{-1}, typical of the $SO_2N{=}C$- group.[3-6]

The products from base treatment of **1** are shown in Table II and their physical properties in Tables III and IV. The dihydrothiadiazines have similar infrared and nmr spectra to those reported recently.[3] The *N*-styrylamidine salts have typical amidinium absorptions[7,8] in their infrared spectra, with strong bands at ~1675 ($C{=}N^+$) and ~3000 cm^{-1} (NH). In the nmr spectra (DMSO-d_6) the NH protons appear as broad signals, close to δ 10.0 (1 H) and 12.0 (2 H), and they undergo exchange on addition of D_2O. The trans vinylic protons in these compounds appear as doublets ($J \simeq 14.0$ Hz) at about δ 6.8 and 8.0. In spectra of the *N*-styrylamidine free bases, these doublets are shifted upfield to about δ 6.2 and 7.4, respectively, consistent with the values reported by Advani, *et al.*[9]

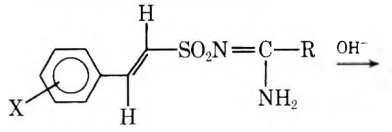
Treatment of the unsubstituted *N*-(styrylsulfonyl)amidines **1a** and **1b** with NaOH in DMSO for 64 hr at 25° gave the expected 5-phenyl-5,6-dihydro-4*H*-1,2,4-thiadiazine 1,1-dioxides **2a** and **2b** in high yields along with small amounts of the corresponding *N*-(*trans*-styryl)amidines **3a** and **3b.** The monochloro-*N*-(styrylsulfonyl)amidine **1c** afforded a relatively larger amount of styrylamidine **3c,** whereas the 3,4-dichloro derivatives **1d** and **1e** gave high yields of *N*-styrylamidines **3d** and **3e** with only traces of the corresponding dihydrothiadiazines **2d** and **2e.** Some unreacted starting material was recovered from these reactions even after 64 hr and lower yields of products were obtained after shorter reaction times. The phenylacetamidine

Table III
5-Aryl-5,6-dihydro-4*H*-1,2,4-thiadiazine 1,1-Dioxides (2)

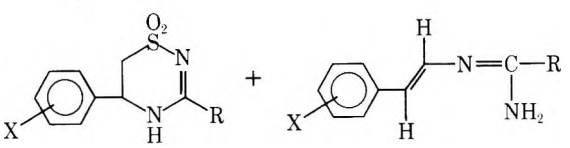


Compd	X	R	Mp, °C	Crystn solvent	Formula
2a	H	Me	276.5–278.5	MeCN	$C_{10}H_{12}N_2O_2S$
2b	H	Ph	235.5–236.5	MeCN	$C_{15}H_{14}N_2O_2S$
2c	4-Cl	Me	274.5–277.5	Me_2CO–*i*-Pr_2O	$C_{10}H_{11}ClN_2O_2S$
2d	3,4-Cl_2	Me	257–259.5	MeOH	$C_{10}H_{10}Cl_2N_2O_2S$
2e	3,4-Cl_2	Ph	300–301	MeOH	$C_{15}H_{12}Cl_2N_2O_2S$
2f	3,4-Cl_2	$PhCH_2$	282.5–284	MeOH	$C_{16}H_{14}Cl_2N_2O_2S$

of products formed by base treatment of **1** and the mechanisms of formation of these products.



1



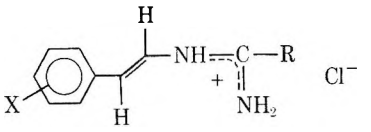
2 3

The *N*-(*trans*-styrylsulfonyl)amidines (**1,** Table I) were obtained by reaction of the appropriate amidine with a *trans*-styrylsulfonyl chloride.[2] The infrared spectra of these compounds show strong absorption at 1635–1655

1f also rearranged to a *N*-styrylamidine (**3f**) under these conditions, but afforded only the dihydrothiadiazine **2f** when the reaction was carried out in acetone. Treatment of *N*-(2- or 4-nitrostyrylsulfonyl)amidines **1g–j** with NaOH in DMSO or acetone caused rapid rearrangement (<1 hr) to *N*-styrylamidines **3g–j.** It is apparent, therefore, that this rearrangement is facilitated by electron-withdrawing aromatic substituents and by solvents of high polarity.

Likely mechanisms for the formation of dihydrothiadiazines (**2**) and *N*-styrylamidines (**3**) are shown in Scheme I. Base treatment of sulfonylamidine **1** affords an anion which may be drawn as the resonance structures **4a** and **4b.** The N anion in **4b** may attack the C atom either α or β to the sulfonyl group to give the carbanion **7** or **5,** respectively. With an unsubstituted aromatic ring, the carbanion **5** is apparently preferred to **7,** and a dihydrothiadiazine **2** is the major product. However the presence of electron-withdrawing substituents in the aromatic ring would stabilize **7**

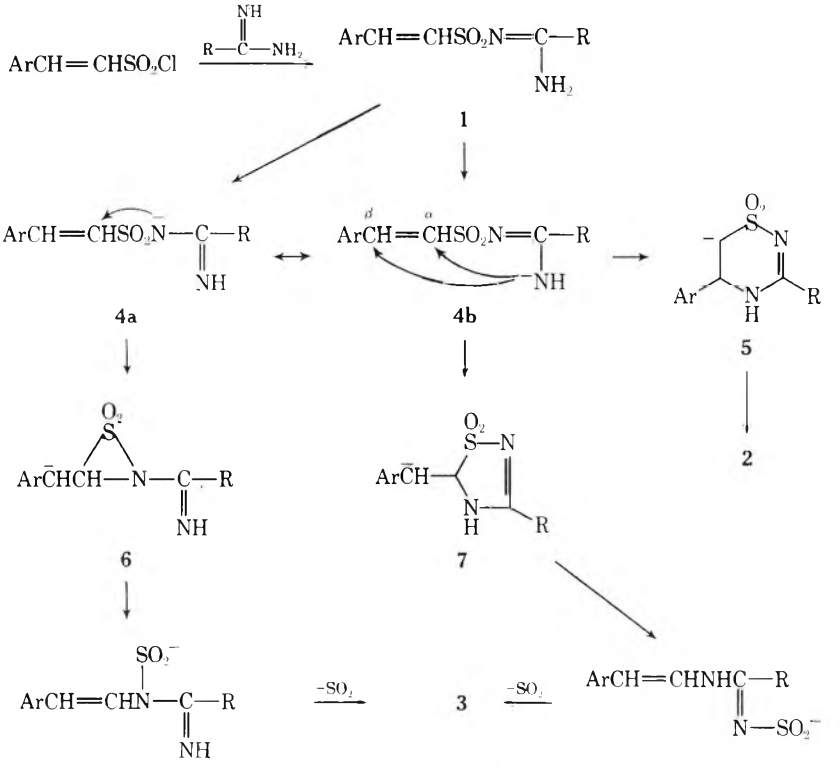
Table IV
N-(*trans*-Styryl)amidines (3)



Compd	X	R	Mp,[a] °C	Crystn solvent	Formula
3a	H	Me	167–183	*i*-PrOH	$C_{10}H_{13}ClN_2$
3b	H	Ph	226.5–228	MeOH–*i*-Pr_2O	$C_{15}H_{15}ClN_2$
3c	4-Cl	Me	228–234.5	MeOH–*i*-Pr_2O	$C_{10}H_{12}Cl_2N_2$
3d	3,4-Cl_2	Me	215–224	MeOH–*i*-Pr_2O	$C_{10}H_{11}Cl_3N_2$
3e	3,4-Cl_2	Ph	243–248.5	EtOH–MeOH–*i*-Pr_2O	$C_{15}H_{13}Cl_3N_2$
3f	3,4-Cl_2	$PhCH_2$	216–219	*i*-PrOH	$C_{18}H_{20}Cl_2N_2O_4S$[b]
3g	4-NO_2	Me	247–247.5	MeOH	$C_{10}H_{12}ClN_3O_2$
3h	4-NO_2	Ph	255–257	MeCN	$C_{17}H_{19}N_3O_6S$[c]
3i	2-NO_2	Me	227–229	EtOH–*i*-Pr_2O	$C_{10}H_{12}ClN_3O_2$
3j	2-NO_2	Ph	219.5–221.5	MeOH–*i*-Pr_2O	$C_{15}H_{14}ClN_3O_2$

[a] The crude free bases of the following compounds were isolated as solids: **3c**, mp 134–136°; 3d, mp 125–128°; **3g**, mp 142–143°; **3h**, mp 160–162°. [b] Analyses were obtained on the isethionate salt, mp 132.5–134.5° (MeCN). [c] Analyses were obtained on the isethionate salt, mp 204–206.5° (MeOH–*i*-Pr_2O).

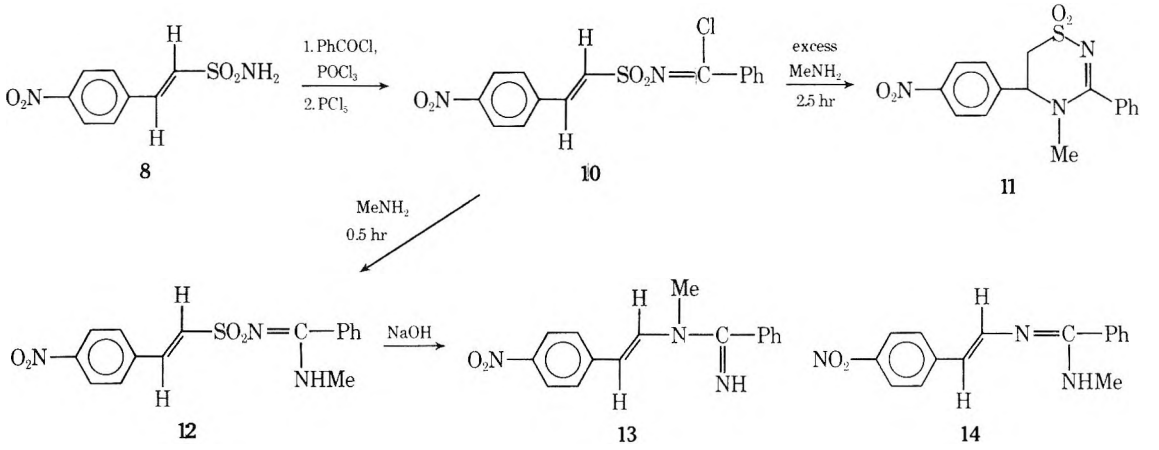
Scheme I



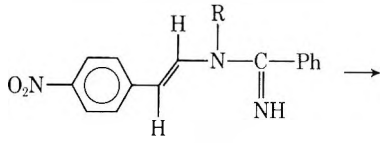
by delocalization of the negative charge and the intermediate **7** would be preferred over **5**. This five-membered heterocycle may then break down to afford a *N*-styrylamidine **3** by β-elimination of the SO_2 group followed by hydrolysis of the resulting *N*-sulfonyl intermediate. A somewhat analogous intramolecular attack in 4-nitrobenzenesulfonyl guanidines has been described.[10-12] Alternatively, *N*-styrylamidines **3** could form from **4a**, *via* a Ramberg–Bäcklund type of intramolecular reaction,[13] to afford a three-membered ring intermediate **6**, which could then undergo ring opening and elimination of SO_2.

In order to distinguish between these two routes to *N*-styrylamidines, we prepared *N*-methyl-*N'*-(4-nitrostyrylsulfonyl)benzamidine **12** as shown in Scheme II, and studied its rearrangement with base. The chloroimidate **10** was obtained by a method similar to that of Lawson and Tinkler,[14] but treatment of **10** with excess methylamine in acetone for 2.5 hr gave the dihydrothiadiazine **11** instead of the sulfonylamidine **12**. Apparently, under these conditions, the initially formed **12** underwent cyclization to **11**. This is the only instance of dihydrothiadiazine formation from nitro-substituted *N*-(styrylsulfonyl)amidines that we have observed. When we treated **10** with a limited amount of methylamine for a short time, we obtained the desired sulfonylamidine **12**, which was converted to *N*-methyl-*N*-(*trans*-4-nitrostyryl)benzamidine **13** by NaOH in acetone. This is the product expected from the route involving a five-membered ring intermediate.

Scheme II

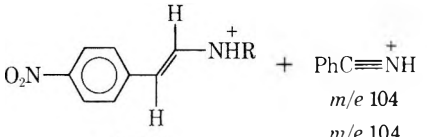


It is distinguishable by nmr and mass spectra from **14**, the product expected from the alternate three-membered intermediate. In the nmr spectrum of **13** in DMSO-d_6, no coupling of the *N*-methyl protons is observed, in contrast to the doublet observed for the *N*-methyl protons of **12**. The major fragments in the mass spectra of **13** and **3** appear to be due to the molecular ions, PhC≡NH$^+$, and 4-nitrostyrylamine fragments in agreement with the fragmentation pattern of *N*-phenylbenzamidines.[15] The



3, R = H, *m/e* 267

13, R = Me, *m/e* 281



m/e 164

m/e 178

m/e 104

m/e 104

styrylamine fragment with *m/e* 178 is consistent with that expected from **13** but not from **14**. The absence of a PhC≡N$^+$–Me fragment is also consistent with structure **13**.

This rearrangement of *N*-(*trans*-styrylsulfonyl)amidines is, therefore, analogous to a Smiles arrangement[10] in which the intramolecular nucleophilic attack occurs on a vinylic carbon rather than an aromatic carbon. The scope of the reaction may be similar to that of the Smiles rearrangement.[10]

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. Nmr data were obtained with a Varian A-60A or XL-100 spectrometer with tetramethylsilane as an internal standard. Mass spectra were measured on a Varian MAT 311 spectrometer. Microanalytical and spectral data were supplied by the Physical Analytical Department of Mead Johnson & Co. Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds. The styrylsulfonyl chlorides used in this work were obtained by previously described methods.[2] Phenylacetamidine benzenesulfonate was prepared by the method of Oxley and Short.[16] *trans*-4-Nitrostyrylsulfonamide (**9**) was obtained by the method of Bordwell, *et al.*[17]

***N*-(*trans*-Styrylsulfonyl)acetamidine (1a).** A mixture of acetamidine hydrochloride (14.2 g, 0.15 mol) and 50% aqueous NaOH (12.0 g, 0.15 mol) in acetone (200 ml) was stirred vigorously for 10 min and then cooled to 10° in an ice bath. Finely powdered *trans*-styrylsulfonyl chloride (10.1 g, 0.05 mol) was then added, in portions, at such a rate as to maintain the reaction temperature at about 10°. The mixture was stirred for an additional 10 min and then concentrated under reduced pressure. Water (100 ml) was added to the residue and the mixture was acidified with 3 *N* HCl. Insoluble solid was collected by filtration, washed with water, air dried, and crystallized from *i*-PrOAc to afford 8.5 g (76%) of **1a** as white crystals: nmr ($CDCl_3$) δ 7.84 (broad s, 1, NH), 7.64 (d, 2, J = 15.5 Hz, =CH), 7.45 (m, 5, ArH), 6.92 (d, 2, J = 15.5 Hz, =CH), 6.73 (broad s, 1, NH), 2.16 (s, 3, CH_3); ir (KBr) 3435, 3335, 3250 (NH), 1645 (NH_2), 1550 (C=N), 1270, 1130 cm^{-1} (SO_2).

Other *N*-(styrylsulfonyl)amidines in Table I were prepared by similar procedures. Reaction of *trans*-2-nitrostyrylsulfonyl chloride with benzamidine, according to this procedure, failed to afford a solid product **1j**. The crude **1j** was extracted into $CHCl_3$ and converted to **3j** by treatment with NaOH in Me_2CO (method B below).

Base Treatment of *N*-(*trans*-Styrylsulfonyl)amidines. A. In DMSO. *N*-(*trans*-Styrylsulfonyl)benzamidine (**1b**) (4.3 g, 0.015 mol) was added in portions to a stirred mixture of 50% aqueous NaOH (1.2 g, 0.015 mol) in DMSO (25 ml). The mixture was stirred at 25° for 64 hr, poured into cold water (250 ml), and made strongly basic with 5% aqueous NaOH. It was extracted several times with ether and the extracts were washed with water and dried (K_2CO_3). Evaporation of the solvent gave a yellow oil that formed a salt with ethanolic HCl. The crude salt was triturated with acetone and crystallized to afford 0.25 g (6.5%) of ***N*-(*trans*-styryl)benzamidine hydrochloride (3b):** nmr (DMSO-d_6) δ 12.03 (broad s, 1, NH), 10.33 (broad, 2, NH_2), 8.25 (d, 1, J = 14.0 Hz, =CH), 8.0–7.1 (m, 10, ArH), 6.95 (d, 1, J = 14.0 Hz, =CH); ir (KBr) ~3050 (broad, NH), 1665 cm^{-1} (broad, C=N).

Acidification of the aqueous alkaline fraction with 3 *N* HCl precipitated a white solid, which was washed with water, air dried, and crystallized to afford 2.3 g (84%) of **5,6-dihydro-3,5-diphenyl-4*H*-1,2,4-thiadiazine 1,1-dioxide (2b):** nmr (DMSO-d_6) δ 9.67 (broad s, 1, NH), 7.93 and 7.55 (m, 10, ArH), 5.17 (dd, 1, J = 5.5, 11.5 Hz, CH), 3.47 (m, 2, CH_2); ir (KBr) 3310 (NH), 1550 (C=N), 1300 and 1130 cm^{-1} (SO_2).

Compounds **2a–e** in Table III and **3a–f** in Table IV were obtained in similar procedures.

B. In Acetone. A suspension of *N*-(*trans*-4-nitrostyrylsulfonyl)benzamidine (**1h**, 9.9 g, 0.03 mol) in acetone (100 ml) was stirred with 50% aqueous NaOH (8.0 g, 0.1 mol) in water (20 ml) for 1 hr. Evaporation of the solvent left an orange-red solid that was stirred with water (50 ml), filtered, washed thoroughly with water, and air dried. Trituration of the solid with 2-propanol afforded 7.7 g (96%) of *N*-(*trans*-4-nitrostyryl)benzamidine (**3h**): mp 160–162°; nmr (DMSO-d_6) δ 8.3–7.0 (m, 12, ArH, =CH, NH), 6.40 (d, 1, J = 14.0 Hz, =CH); ir (KBr) 3470, 3315, 3200 (NH), 1625, 1550 (C=N), 1505 and 1345 cm^{-1} (NO_2); mass spectrum *m/e* (rel intensity) 267 (30, M$^+$), 234 (60), 164 (35, M – PhC≡N), 104 (100, PhC≡NH$^+$). A portion of this solid, in hot acetonitrile, was acidified with ethanolic HCl. On cooling, the solution **3h** separated as yellow crystals: nmr (DMSO-d_6) δ 11.83 (broad s, 1, NH), 10.17 (broad s, 2, NH_2), 8.50 (d, 1, J = 14.0 Hz, =CH), 8.24 (d, 2, J = 9.0 Hz, ArH), 8.0–7.5 (m, 5, ArH), 7.70 (d, 2, J = 9.0 Hz, ArH), 6.97 (d, 1, J = 14.0 Hz, =CH); ir (KBr) 3020 (broad, NH), 1670 cm^{-1} (broad, C=N).

The *N*-styrylamidines **3i** and **3j** in Table IV were obtained in similar procedures. The free bases of these compounds were isolat-

ed as oils on evaporation of the reaction solvent. They were extracted into chloroform, washed with water, dried (K_2CO_3), and converted to hydrochloride salts. By a similar procedure, the dihydrothiadiazine **2f** (Table III) was obtained after a 24-hr reaction time by extraction of the crude product into ethyl acetate, evaporation of the solvent, and trituration of the residue with hot ethanol.

N-(*trans*-**4-Nitrostyrylsulfonyl)benzamide (9).** A mixture of *trans*-4-nitrostyrylsulfonamide (18.2 g, 0.08 mol), benzoyl chloride (12.6 g, 0.09 mol), and $POCl_3$ (13.8 g, 0.09 mol) was heated on a steam bath for 1.5 hr. The mixture was then diluted with ethyl acetate (20 ml), cooled, and filtered to afford 19.0 g (76%) of yellow solid **9:** mp 192–195° (ethyl acetate–hexane); ir (KBr) 3290 (NH), 1685 cm^{-1} (C=O). *Anal.* Calcd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.64; N, 8.43. Found: C, 53.86; H, 3.63; N, 8.28.

N-(*trans*-**4-Nitrostyrylsulfonyl)benzimidoyl Chloride (10).** A suspension of **9** (14.9 g, 0.045 mol) in dry benzene (500 ml) was refluxed and stirred with PCl_5 (10.4 g, 0.05 mol) for 8 hr. The resulting solution was allowed to stand overnight at 25° and afforded 8.2 g of pale-yellow solid, mp 158–166°. Concentration of the filtrate to about 100 ml gave an additional 2.5 g of solid, mp 158–161°. Crystallization of the crude product from ethyl acetate gave analytically pure **10,** mp 168–175°. *Anal.* Calcd for $C_{15}H_{11}ClN_2O_4S$: C, 51.36; H, 3.16; N, 7.99. Found: C, 51.46; H, 3.09; N, 7.79.

5,6-Dihydro-4-methyl-5-(4-nitrophenyl)-3-phenyl-1,2,4-thiadiazine 1,1-Dioxide (11). Methylamine was bubbled into a solution of **10** (5.25 g, 0.015 mol) in acetone (100 ml) for 2.5 hr. The red solution was concentrated under reduced pressure, diluted with water (50 ml), and acidified with 3 *N* HCl. The mixture was stirred for several minutes and insoluble product was collected by filtration and air dried. After trituration of the solid with 2-propanol (30 ml) and then isopropyl ether, 3.2 g (61%) of **11** was obtained as a pink solid: mp 179.5–181° dec after crystallization from acetonitrile; nmr (DMSO-d_6) δ 8.15 (d, 2, J = 8.5 Hz, ArH), 7.66 (d, 2, J = 8.5 Hz, ArH), 7.50 (s, 2, =CH), 5.03 (dd, 1, J = 8.5, 6.0 Hz, CH), 3.40 (m, 2, CH_2), 3.02 (s, 3, NCH_3); ir (KBr) 1530 (broad, C=N) 1315 and 1165 cm^{-1} (SO_2). *Anal.* Calcd for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17. Found: C, 55.77; H, 4.32; N, 12.23.

N-**Methyl**-*N'*-(*trans*-**4-nitrostyrylsulfonyl)benzamidine (12).** Methylamine was passed slowly into a solution of **10** (6.3 g, 0.018 mol) in dry acetone (50 ml) for 5 min at 25°. The mixture was stirred for another 25 min at 25° and then concentrated. Water (50 ml) and chloroform (150 ml) were added and the mixture was shaken vigorously and then filtered. Insoluble material was stirred and heated with chloroform (200 ml) and then cooled. Filtration of insoluble material gave 0.6 g of **12.** The chloroform filtrates were combined, washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Trituration of the residue with methanol afforded an additional 3.5 g of **12.** A sample crystallized from acetonitrile to give analytically pure **12:** mp 155.5–157° dec; nmr (DMSO-d_6) δ 9.00 (broad s, 1, NH), 8.21 (d, 2, J = 9.0 Hz, ArH), 7.85 (d, 2, J= 9.0 Hz, ArH), 7.70–7.25 (m, 6, ArH and =CH), 7.12 (d, 1, J = 15.0 Hz, =CH), 2.92 (d, 3, J = 4.0 Hz, NCH_3); ir (KBr) 3235 (broad, NH), 1550 (broad, C=N), 1345 and 1120 cm^{-1} (SO_2). *Anal.* Calcd for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17. Found: C, 55.29; H, 4.24; N, 12.16.

N-**Methyl**-*N*-(*trans*-**4-nitrostyryl)benzamidine Hydrochloride (13).** A mixture of **12** (3.45 g, 0.01 mol) and 10% aqueous NaOH (25 ml) in acetone (100 ml) was stirred at 25° for 30 min. The solvent was removed under reduced pressure and the residue was diluted with water and extracted into chloroform. The extract was washed with water, dried (K_2CO_3), and concentrated to a red oil, which formed a salt with ethanolic HCl. Trituration of the crude salt with acetone and crystallization from methanol–isopropyl ether afforded 2.4 g (75%) of **13** as a pale-yellow solid: mp 247.5–249.5° dec; nmr (DMSO-d_6) δ 10.70 (broad s, 2, NH_2), 8.22 (d, 2, J = 9.0 Hz, ArH), 8.0–7.6 (m, 8, ArH, =CH), 6.90 (d, 1, J = 14.0 Hz, =CH), 3.44 (s, 3, NCH_3); ir (KBr) 2940 (broad, NH), 1675 and 1650 cm^{-1} (C=N). *Anal.* Calcd for $C_{16}H_{16}ClN_3O_2$: C, 60.47, H, 5.08; N, 13.22. Found: C, 60.66; H, 5.03; N, 13.35.

A sample of **13** was converted to the free base by 10% aqueous NaOH in methanol. The solution was concentrated and the free base was extracted into chloroform, washed with water, and dried (K_2CO_3). Evaporation of the solvent gave the orange free base of **13:** mp 105–110°; nmr ($CDCl_3$) δ 8.01 (d, 2, J = 9.0 Hz, ArH), 7.54 (d, 1, J = 14.0 Hz, =CH), 7.6–7.3 (m, 6, ArH, NH), 7.14 (d, 2, J = 9 Hz, ArH), 5.77 (d, 1, J = 14.0 Hz, =CH), 3.32 (s, 3, NCH_3); ir (KBr) 3315 (NH), 1635, 1590 (C=N), 1505 and 1330 cm^{-1} (NO_2); mass spectrum *m/e* (rel intensity) 281 (22, M^+), 178 (35, M − PhC≡N), 159 (25), 104 (100, PhC≡NH^+).

Registry No.—**1a,** 52147-70-3; **1b,** 52147-71-4; **1c,** 52196-19-7; **1d,** 52147-72-5; **1e,** 52196-20-0; **1f,** 52147-73-6; **1g,** 52147-74-7; **1h,** 52147-75-8; **1i,** 52147-76-9; **2a,** 52148-03-5; **2b,** 52148-04-6; **2c,** 52148-05-7; **2d,** 52148-06-8; **2e,** 52148-07-9; **2f,** 52148-08-0; **3a,** 52147-77-0; **3b,** 52147-78-1; **3c,** 52147-79-2; **3c** (free base), 52147-80-5; **3d,** 52147-81-6; **3d** (free base), 52147-82-7; **3e,** 52147-83-8; **3f,** 52147-85-0; **3g,** 52194-04-4; **3g** (free base), 52147-86-1; **3h,** 52147-88-3; **3h** (free base), 52147-87-2; **3i,** 52147-89-4; **3j,** 52147-90-7; **8,** 52147-91-8; **9,** 52147-92-9; **10,** 52147-93-0; **11,** 52148-09-1; **12,** 52147-94-1; **13,** 52147-95-2; **13** (free base), 52147-96-3; ArCH=CH-SO_2Cl (Ar = Ph), 52147-97-4; ArCH=$CHSO_2Cl$ (Ar = 4-ClC_6H_4), 52147-98-5; ArCH=$CHSO_2Cl$ (Ar = 3,4-$Cl_2C_6H_3$), 52147-99-6; Ar-CH=$CHSO_2Cl$ (Ar = 4-$NO_2C_6H_4$), 52148-00-2; ArCH=$CHSO_2Cl$ (Ar = 2-$NO_2C_6H_4$), 52148-01-3; RC(NH)NH_2 (R = Me), 143-37-3; RC(NH)NH_2 (R = Ph), 618-39-3; RC(NH)NH_2 (R = $PhCH_2$), 5504-24-5.

References and Notes

(1) Presented in part at the Fourth International Congress of Heterocyclic Chemistry, Salt Lake City, Utah, July 8, 1973.
(2) W. L. Matier, W. T. Comer, and A. W. Gomoll, *J. Med. Chem.*, **17,** 549 (1974).
(3) K. Hasegawa and S. Hirooka, *Bull. Chem. Soc. Jap.*, **45,** 1893 (1972).
(4) J. Danilewicz, M. J. Sewell, and J. C. Thurman, *J. Chem. Soc. C,* 1704 (1971).
(5) G. Schwenker and K. Bosl, *Arch. Pharm. (Weinheim),* **303,** 980 (1970).
(6) R. B. Tinkler, *J. Chem. Soc. B,* 1052 (1970).
(7) J. C. Grivas and A. Taurins, *Can. J. Chem.*, **37,** 1260 (1959).
(8) P. Bassignana, C. Cogrossi, G. Polla-Mattiot, and S. Franco, *Ann. Chim. (Rome),* **53,** 1212 (1963).
(9) B. G. Advani, K. Nagarajan, P. Rajagopalan, and V. Ranga Rao, *Tetrahedron Lett.*, 5825 (1968).
(10) W. E. Truce, E. M. Kreider, and W. W. Brand, *Org. React.*, **18,** 99 (1970).
(11) H. J. Backer and H. D. Moed, *Recl. Trav. Chim. Pays-Bas,* **66,** 689 (1947).
(12) H. J. Backer and S. K. Wadman, *Recl. Trav. Chim. Pays-Bas,* **68,** 595 (1949).
(13) F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, **73,** 5187 (1951), and references cited therein.
(14) A. Lawson and R. B. Tinkler, *J. Chem. Soc. C,* 1429 (1970).
(15) J. A. Gautier, M. Miocque, C. Fauran, and A. Y. Le Cloarec, *Bull. Soc. Chim. Fr.*, 478 (1971).
(16) P. Oxley and W. F. Short, *J. Chem. Soc.*, 147 (1946).
(17) F. G. Bordwell, A. B. Colbert and B. Alan, *J. Amer. Chem. Soc.*, **68,** 1778 (1946).

Kinetics and Mechanism of Tetrazole Formation from 1-Adamantyl Arenesulfonates in Acetonitrile Containing Azide Ion[1]

Dennis N. Kevill* and Chang-Bae Kim

Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115

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The reactions of seven 1-adamantyl arenesulfonates with 0.12–0.48 *M* solutions of tetraethylammonium azide in acetonitrile give predominantly (>80%) 1-(1-adamantyl)-5-methyltetrazole (by solvolysis followed by 1,3-addition of azide ion) and smaller amounts of the direct substitution product, 1-adamantyl azide. The product distribution is essentially independent of the identity of the arenesulfonate leaving group and it follows the mathematical form required by competition for an intermediate between azide ion and solvent. The kinetics are, except for relatively small salt effects, independent of the concentration of azide ion and the rates, with 0.08 *M* tetraethylammonium azide at 25°, are some 5–17 times slower than for corresponding ethanolyses; it is shown that this is primarily due to a reduction in the entropy of activation. At 25°, the Hammett ρ value of 2.34 ± 0.10 is appreciably larger than the 1.76 ± 0.08 for ethanolysis, consistent with the usual magnification of leaving-group effects upon going from a protic to an aprotic solvent. As in ethanolysis, there is a deviation from "normal" behavior in that the *m*-nitro derivative reacts faster than the *p*-nitro derivative.

In hydroxylic solvents, azide ion has for many years been used as a probe for the mechanism of the solvolysis of added substrates.[2-8] In particular, for reactions proceeding *via* an intermediate carbonium ion or ion pair, the ratios of the second-order rate coefficients for capture by either solvent or azide ion have been logarithmically plotted against the solvolysis rates to give stability–selectivity linear free energy correlations.[3,4] The more stable carbonium ions show both the faster rates of formation and also the greater selectivity toward nucleophilic capture.

In hydroxylic solvents, the rapid deprotonation of the first formed oxonium ion (to give a relatively stable alcohol or ether) by another solvent molecule, by the azide ion, or by the leaving group prevents complications which could otherwise arise from further reaction of the oxonium ion, as in the case of attack by dioxane when such reaction cannot operate.[5] However, the presence of this acidic proton can lead, as pointed out by Ritchie,[6] to complications of a different type, in that the possibility exists of a general base catalysis to the capture of the carbonium ion intermediate by the solvent. Ritchie was discussing primarily reactions of relatively stable carbonium ions and he concentrated on the characteristics of general base catalysis by the trapping agent. Harris[9,10] has suggested that, for relatively reactive carbonium ions formed during solvolysis, the catalyst is more likely to be the departing anion, with capture occurring at the solvent-separated ion-pair stage. Evidence has also been presented that, in the solvolysis of benzhydryl derivatives, the intervention by added azide ion can occur at the solvent-separated ion-pair stage.[7,8,11]

Since azide ion incorporation values cannot be taken by themselves as an indication of mechanism,[3] studies with 1-adamantyl and 2-adamantyl derivatives are especially useful; bimolecular attack on 1-adamantyl derivatives is prevented by the cage structure and steric hindrance to an SN2 transition state for 2-adamantyl derivatives leads to little, if any, nucleophilic assistance to its substitution reactions.[12,13] The more subtle details of the substitution mechanisms for adamantyl derivatives are not firmly established, but it is clear that an initial ionization is followed by subsequent attack upon a carbonium ion or ion pair; controversy exists regarding the importance of ion-pair return in these systems and, consequently, as to whether ionization[14] or interconversion of intimate to solvent-separated ion pairs[15] is rate determining.

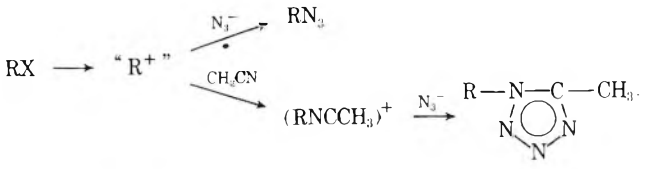
A study has been made[3] of the influence of azide ion upon the solvolysis of 1-adamantyl bromide and 2-adamantyl tosylate in 80% ethanol at 75°. In both instances a modest rate increase was observed, consistent with a salt effect upon a unimolecular solvolysis, and, even with concentrations of sodium azide as high as 0.06 *M*, very little adamantyl azide was formed. Corresponding studies in dipolar aprotic solvents would be of interest. Hydrogen bonding to the departing anion within the solvent-separated ion pair (and general base catalysis) would not be operative and, since these solvents are usually less nucleophilic than hydroxylic solvents and anions dissolved in them are (owing to lack of hydrogen-bonded solvation) considerably more nucleophilic than in hydroxylic solvents, one would predict increased amounts of azide relative to solvolysis product.

A semiquantitative study has been made[16] with 1-adamantyl bromide and sodium azide in dimethyl sulfoxide, dimethylformamide, and hexamethylphosohororamide. Even after 3 days at 100°, no reaction was detected in the latter two solvents but, in dimethyl sulfoxide, a 29.6% yield of 1-adamantyl azide was isolated after 2 days and this rose only to 35.2% after 14 days; about 30% 1-adamantanol was also isolated after water treatment, presumably by hydrolysis of the initial solvolysis product,[17] 1-adamantoxydimethylsulfonium ion $(1\text{-AdOSMe}_2)^+$. The very slow increase in 1-adamantyl azide production after the initial 2-day period suggests that it is primarily formed concurrent with the solvolysis product rather than, as the authors suggested,[16] from it.

In a study of the decomposition of 1-adamantyl chloroformate in a variety of solvents, it was found that in acetonitrile capture of intermediate 1-adamantyl carbonium ions by solvent could compete with collapse to 1-adamantyl chloride; addition of water led to the isolation of *N*-(1-adamantyl)acetamide.[18] However, on remaining in solution for several days, the solvent-capture product underwent replacement of acetonitrile by chloride ion to convert to the alternate 1-adamantyl chloride.[19] The solvolysis product could also be captured by 1,3-addition of azide ion to give 1-(1-adamantyl)-5-methyltetrazole.[19] Indeed, it has been found that even nitrilium cations such as *N*-ethylacetonitrilium ion, which could readily undergo SN2 displacement of nitrile by azide ion, preferentially undergo 1,3-addition.[20] Azide ion in acetonitrile does therefore represent a very useful aprotic system for both kinetic and product partitioning studies. The two possible products, alkyl azide and 1-alkyl-5-methyltetrazole (*via* solvolysis), both consume azide in their production and, since azide is basic to

resorcinol blue (Lacmoid) in aprotic solvents,[21] acid–base titration can be used to monitor the overall kinetics of reaction. Gas chromatography can be used to determine the product ratio. Remaining noncommittal at this stage concerning the actual intermediate (or intermediates) which are trapped, the situation for an ionization reaction will be as in Scheme I.

Scheme I



The substrates employed in the investigation reported at this time are 1-adamantyl benzenesulfonate and six para- or meta-substituted derivatives. The kinetic studies can be compared to parallel ones which were carried out in a hydroxylic solvent, ethanol,[22] and the product ratios can be compared with those obtained for competition between azide ion and solvent for 1-adamantyl bromide and 2-adamantyl tosylate in 80% ethanol[3,23] and related to the mechanism proposed to explain the nature of the partitioning between the two components of the solvent for a series of 2-adamantyl arenesulfonates in aqueous ethanol.[9]

Results

Kinetics of Reaction of 1-Adamantyl Arenesulfonates in Acetonitrile Containing Azide Ion. Acid–base titration was used to follow the disappearance of azide ion[21] and, since the reduction in azide ion concentration is accompanied by a corresponding reduction in 1-adamantyl arenesulfonate concentration, first-order rate coefficients (specific rates) for the reaction of 1-adamantyl arenesulfonate could be calculated. Within experimental error, these coefficients remained constant throughout each run. A study was made, at 25.0°, with varying tetraethylammonium azide concentrations and with 0.1 *M* initial concentrations of the parent 1-adamantyl benzenesulfonate plus the *p*-methoxy, *p*-chloro, *p*-bromo, and *p*-nitro derivatives; a corresponding study was made of the *p*-methyl derivative at 39.6°. A small increase in the specific rate of reaction of the 1-adamantyl arenesulfonate (k^{expt}) was linearly related to the increase in the initial tetraethylammonium azide concentration and the data were treated according to the equation $k^{expt} = k_0(1 + b[NEt_4N_3])$; values for k_0 and b are reported within Table I.

The b values are of the same order of magnitude as those previously reported[23] for 2-adamantyl tosylate in 75% aqueous dioxane (3.5) and 80% aqueous ethanol (3), values which were assumed to reflect salt effects. In order to determine whether this explanation applies to the present systems, several runs were carried out with 0.1 *M* 1-adamantyl *p*-toluenesulfonate and 0.08 *M* tetraethylammonium azide at 39.6°. Addition of either tetraethylammonium perchlorate or tetraethylammonium *p*-toluenesulfonate led to rate increments which were, within experimental error, identical with those obtained upon adding an identical concentration increment of tetraethylammonium azide (Table II), confirming that the acceleration is indeed due to a salt effect. The similar behavior of the azide and *p*-toluenesulfonate salts is consistent with the lack of perturbation throughout each run, when azide ion is being replaced by arenesulfonate ion.

In view of the relatively small sensitivity of the rate to salt concentration, it was decided that, rather than carry out for each system at each temperature a series of runs at several salt concentrations and then extrapolate the specific rates back to very low salt concentration, it would be less time consuming and also slightly more accurate (magnification of errors due to extrapolation avoided) to choose, as a standard medium for further kinetic studies, acetonitrile containing 0.08 *M* tetraethylammonium azide. Values for the specific rate of reaction under these standard conditions of 1-adamantyl benzenesulfonate and the *m*-nitro derivative at 25° and for the *p*-methoxy, *p*-methyl, *p*-chloro, *p*-bromo, and *p*-nitro derivatives at several temperatures within the range 15–60° are reported within Table III together with activation parameters for those derivatives studied over a range of temperatures.

Table I
Kinetic Parameters for Reaction of 0.1 *M* 1-Adamantyl Arenesulfonates in Acetonitrile, Containing Various Concentrations of Azide Ion, at 25.0°

Substituent	$[NEt_4N_3]$, *M*	$10^6 k_0$, sec^{-1} [a]	b, M^{-1} sec^{-1} [a]
p-OMe	0.08–0.30	1.49 ± 0.07	1.6 ± 0.1
p-Me	0.08–0.40		1.4 ± 0.1[b]
None	0.08–0.30	4.49 ± 0.16	1.4 ± 0.1
p-Cl	0.06–0.30	20.2 ± 2.9	2.1 ± 0.1
p-Br	0.08–0.24	21.6 ± 1.8	2.5 ± 0.2
p-NO_2	0.08–0.30	235 ± 23	4.1 ± 0.2

[a] From intercept and slope of plots of experimental first-order rate coefficients *vs.* $[NEt_4N_3]$, with associated standard errors; $k^{expt} = k_0(1 + b[NEt_4N_3])$. [b] At 39.6° and including some experiments with $[NEt_4N_3] = 0.08$ *M* and added NEt_4OTs or NEt_4ClO_4; calculated according to $k^{expt} = k_0(1 + b[salt])$; see Table II.

Table II
Influence of Added Tetraethylammonium Salts upon the Specific Rate of Reaction of 0.1 *M* 1-Adamantyl *p*-Toluenesulfonate with 0.080 *M* Tetraethylammonium Azide in Acetonitrile at 39.6° [a]

	$10^5 k_1$, sec^{-1}						
$[NEt_4X]$	0.000	0.040	0.080	0.160	0.240	0.320	Registry no.
X = OTs	1.59[c]	1.70	1.71	2.01		2.27	733-44-8
X = ClO_4	1.59[c]	1.64	1.74	1.95	2.19		2567-83-1
X = N_3[b]	1.59[c]	1.68	1.71	2.04			993-20-4

[a] Values are averages of two or more runs; standard error associated with each run was usually less than 3% of the value. [b] Total NEt_4N_3 concentration minus 0.080 *M*. [c] From Table III.

Product Studies of the Reactions of 1-Adamantyl Arenesulfonates in Acetonitrile Containing Azide Ion. Studies were carried out at 25.0° in acetonitrile solution containing 0.12 *M* tetraethylammonium azide for the unsubstituted 1-adamantyl benzenesulfonate and for the *p*-methoxy, *p*-methyl, *p*-chloro, *p*-bromo, *m*-nitro, and *p*-nitro derivatives. Studies were also made at higher concentrations, ranging up to 0.48 *M*, for the unsubstituted compound and for the *p*-nitro derivative. The reactions were allowed to go to completion (3 weeks or less) and the products were analyzed by glpc. In all cases, small amounts of 1-adamantanol were found and in several instances it was shown that this concentration of 1-adamantanol was present as an impurity within the initial reaction mixtures. Commercial 1-adamantanol and authentic samples of 1-adamantyl azide[19] and 1-(1-adamantyl)-5-methyltetrazole[19] were available for calibration purposes.

The product data are reported in Table IV, together with values for the competition factor (α), $d[1\text{-}AdN_3]/d[\text{tetrazole}] = \alpha[N_3^-]/19.1$, relating the second-order rate coefficients for capture of an intermediate by azide ion and by

Table III
First-Order Rate Coefficients at Various Temperatures[a,b] and Enthalpies (ΔH^*) and Entropies (ΔS^*) of Activation for Reaction of 0.1 *M* 1-Adamantyl Arenesulfonates in Acetonitrile Containing 0.0800 *M* Tetraethylammonium Azide

Substituent	$10^5 k_1$, sec^{-1} 15.0°	25.0°	30.0°	35.0°	40.0°	50.0°	58.6°	ΔH^*_{298},[h] kcal/mol	ΔS^*_{298},[h] eu	Registry no.
p-OMe		0.165		0.670	1.07	3.84		23.2 ± 0.5	−8.2 ± 1.8	43049-41-8
p-Me	0.0925[c]	(0.251)[d]	0.351[e]		1.59[f]	5.07	12.2	23.0 ± 0.2	−7.6 ± 0.8	16200-57-0
None		0.470								43049-43-0
p-Cl	0.492	2.38		9.24	13.4	45.4		23.0 ± 0.5	−2.4 ± 1.6	43049-45-2
p-Br		2.57	4.60		14.5	47.5		21.7 ± 0.2	−3.5 ± 0.8	43049-46-3
m-NO_2		47.9								43049-47-4
p-NO_2	10.8[g]	33.5		105	176			21.0 ± 0.4	−3.7 ± 1.2	43049-48-5

[a] Values are averages of two or more runs; standard error for the first-order rate coefficient associated with each run was less than 4% of its value. [b] Using Hammett σ values from ref 28, a Hammett ρ value at 25.0° of 2.34 ± 0.10 was calculated; omitting the point for *m*-NO_2, a corresponding value of 2.26 ± 0.08 was obtained. [c] At 18.4°. [d] Interpolated from an Arrhenius plot of data at other temperatures. [e] At 28.4°. [f] At 39.6°. [g] At 16.7°. [h] Errors quoted are standard errors.

Table IV
Percentage Composition of Product from Reaction of 0.1 *M* 1-Adamantyl Arenesulfonates within Acetonitrile Containing Tetraethylammonium Azide at 25.0° and Calculated Values for α, the "Competition Factor"

Substituent	$[NEt_4N_3]$	% composition of product: 1-AdOH[a]	1-AdN_3	1-Ad-N-C-CH_3 (tetrazole)	α[b,c]
p-OMe	0.12	4.1	2.3	93.6	6.6
p-Me	0.12	6.4	2.2	91.4	6.3
None	0.12	2.1	2.8	95.1	8.0
	0.16	2.9	3.8	93.4	6.8
	0.20	1.8	5.1	93.0	6.8
	0.24	3.1	6.4	90.6	7.1
	0.30	1.5	7.5	91.0	6.3
	0.36	2.7	8.9	88.5	6.2
p-Cl	0.12	1.1	2.2	96.7	6.1
p-Br	0.12	8.2	2.4	89.4	7.2
m-NO_2	0.12	3.2	2.3	94.5	6.5
p-NO_2	0.12	2.7	2.4	94.9	6.7
	0.24	7.0	5.7	87.3	6.5
	0.36	9.4	7.9	82.8	5.7
	0.48	7.9	10.5	81.6	5.7

[a] In several instances it was shown, by glpc, that these same percentages of 1-adamantanol were present as impurity within the initial reaction mixtures. [b] Defined by $d[1\text{-}AdN_3]/d[\text{tetrazole}] = \alpha[N_3^-]/19.1$ (see ref 24). [c] Based on all entries, the average value is 6.6 ± 0.6; based on experiments with 0.12 *M* NEt_4N_3, the average value is 6.8 ± 0.6.

the solvent acetonitrile (considered as being 19.1 *M*). In calculating competition factor values, allowance was made for consumption of azide ion within both of the competing product-formation steps.[24]

Discussion

The Hammett ρ values of 2.34 ± 0.10, using all the data points, and 2.26 ± 0.08, using only the para-substituted derivatives (omitting the *m*-nitro value), are appreciably larger than the corresponding values of 1.76 ± 0.08 and 1.65 ± 0.07 obtained in ethanolysis.[22] This provides yet another example of the magnification of leaving-group effects observed on transfer of a reaction from a protic to an aprotic solvent.[25,26] As for the ethanolysis,[22] the *m*-nitro derivative reacted faster than the *p*-nitro derivative, presumably once again owing to a solvent effect upon the substituent constants.[27] The Hammett σ values (substituent constants) necessary to place the *m*-NO_2 and *p*-NO_2 derivatives upon the Hammett plot were calculated as +0.80 and +0.73, quite similar to the values of +0.78 and +0.69 obtained in ethanol[22] and quite different from the generally accepted values[28] of +0.71 and +0.78.

The actual rates, at 25°, varied from 16.5 times slower than in ethanol for the *p*-methoxy derivative to 4.4 times slower than in ethanol for both the *m*-nitro and *p*-nitro derivatives. A comparison of the activation parameters (Table III) with those obtained in ethanol[22] shows that, in general, the energy of activation values are comparable (22.0–23.8 kcal/mol in ethanol), with on the average slightly lower values in acetonitrile. Parallel to what was shown for the related ionization reactions of *tert*-butyl derivatives,[26] the slower reaction in acetonitrile results from a considerable lowering of the entropy of activation; for the 1-adamantyl arenesulfonates considered within Table III, the entropies of activation are some 3–8 eu less than for the corresponding ethanolyses.

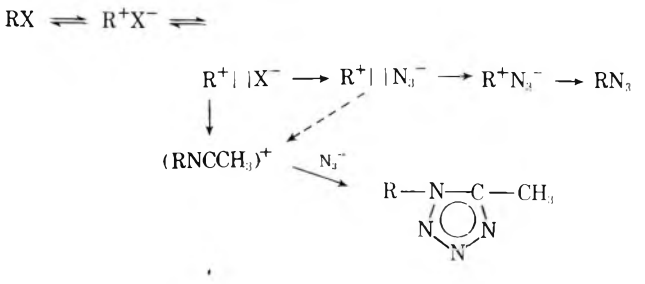
Analysis of the data reported in Table IV shows that a reasonably constant value is obtained for the competition factor and the production of 1-adamantyl azide and 1-(1-adamantyl)-5-methyltetrazole obeys the mathematical form predicted for a competition for an intermediate between azide ions and solvent molecules. The competition factor has an average value of 6.6 ± 0.6, which can be compared to values, for competition between the water component and azide ion in 80% ethanol at 75%, of 2.5 for 1-adamantyl bromide and 1.7 for 2-adamantyl *p*-toluenesulfonate.[3] It must, however, be borne in mind that, in aqueous ethanol, it has been shown that the product partitioning is sensitive to the nature of the leaving group[9] and especially large leaving-group effects upon product partitioning are operative if one is comparing arenesulfonates and halides.[10,29] There can be no doubt, however, that even with a common leaving group all three values would remain very small (for substrates producing relatively stable carbonium ions, competition factors as large as 10^3 have been observed[3]). It is somewhat surprising that a change in solvent from 80% aqueous ethanol to acetonitrile does not lead to an appreciable increase in value. There is evidence that both components of 80% ethanol are considerably more nucleophilic than acetonitrile[8,30] and, in addition, anions have their nucleophilicities considerably increased on transfer

from a protic to an aprotic solvent, presumably owing to elimination of hydrogen-bonded solvation.[33]

The answer to this apparent anomaly may well lie in the competition occurring not for free carbonium ions but for carbonium ions within a solvent-separated ion pair, in which case the mathematical form will parallel that operative for attack on free carbonium ions but, assuming that the solvent molecules capturing the carbonium ion are from the one or two[34] solvent molecules separating the ions, the physical significance of the competition factor value will be quite different. It was shown several years ago that, in the solvolysis of benzhydryl derivatives, capture by added azide ions is probably at the solvent-separated ion-pair stage,[7,8] and, more recently, it has been shown that in 80% ethanol, 2-adamantyl arenesulfonate solvolysis probably also involves capture of the carbonium ion (to give either ether or alcohol) at the solvent-separated ion-pair stage.[9,10] Also, the suggestion that the reactions involve rate-determining conversion from the intimate (contact) to the solvent-separated ion pair[15] would be consistent with capture at this stage. It should be pointed out that one otherwise attractive scheme, involving either collapse with a solvent molecule within the solvent-separated ion pair or separation to give a free carbonium ion which is usually captured by azide ion, is not consistent with the experimental finding of a dependence of the product ratio upon azide ion concentration. While several schemes are possible, it is necessary for the azide ion to be actively involved in forming 1-adamantyl azide, rather than for it to be passively waiting for the production of an intermediate which then prefers to react with azide ion rather than solvent.

A competition at the solvent-separated ion-pair stage would be expected to be strongly biased in favor of solvolysis. Not only are the solvent molecules strategically located but additional bias in their favor can result, in the case of protic solvents, from general base catalysis to the solvolysis[6] by the departing anion.[9,10] For competition between acetonitrile and azide, one can explain our experimental results as in Scheme II. For consistency with the observed mathematical form, it is necessary to assume that little collapse of the carbonium ion with the solvent occurs in $R^+||N_3^-$ and that this entity usually proceeds to RN_3. Under these conditions, low values for the competition factor would not be surprising and, indeed, the theoretical lower limit of unity[3] which would result from competition for a *free* carbonium ion between *free* azide ions and solvent will not apply for a competition of this type and values below unity and all the way down to zero could be observed.[35]

Scheme II



The explanation given[9,10] for the variation in product ratio between ether and alcohol, upon varying the substituent within a series of para-substituted 2-adamantyl arenesulfonates, in terms of hydrogen bonding to the anion being assisted both by electron-supplying substituents and by the presence of two hydrogens in water (cyclic intermediate) as opposed to only one in ethanol requires that, in a mixture of two aprotic solvents, a constant value would be observed for the ratio. An experiment of this type has not yet been performed but the constant product ratio observed, in the present study, for competition between an aprotic solvent, acetonitrile, and added azide ion is consistent with the hydrogen-bonding explanation for variations within mixed protic solvents.[9,10]

Experimental Section

Materials. Acetonitrile was purified as described previously.[36] The preparation and characterization of the 1-adamantyl arenesulfonates has previously been described.[22,37] Samples of 1-adamantyl azide and 1-(1-adamantyl)-5-methyltetrazole, for use as standards, were available from a previous study.[19]

Tetraethylammonium azide was prepared from commercially available tetraethylammonium hydroxide (15% in water) and a solution of hydrazoic acid in either benzene or chloroform.[38] The aqueous layer was evaporated to dryness under reduced pressure and the impure tetraethylammonium azide residue was recrystallized from acetone and dried at 100° under vacuum for 12 hr. The dried salt was immediately dissolved in acetonitrile and the concentration of the solution was determined by titration of aliquots, in acetone against a standardized solution of methanolic hydrogen chloride, using resorcinol blue (Lacmoid) as indicator.[21]

Kinetic Procedures. Solutions of tetraethylammonium azide in acetonitrile of the required concentration were made by appropriate dilution of a stock solution and added to weighed amounts (to make an approximately 0.1 *M* solution) of the appropriate 1-adamantyl arenesulfonate, contained within a 25-ml volumetric flask and maintained at the desired temperature. After temperature equilibration, the reaction was monitored by transfer at convenient time intervals of 2-ml aliquots into acetone and the remaining azide ion concentration was determined by titration, as indicated above. Changes in azide ion concentration were equated to corresponding changes in the concentration of the sulfonate esters and rate coefficients for disappearance of the 1-adamantyl arenesulfonate were obtained by use of the standard form for the integrated first-order rate coefficient. Three illustrative runs are given in Table V.

Product Studies. These were usually carried out using samples of 1-adamantyl arenesulfonates from which several portions had been removed for kinetic studies. Owing to the sensitivity of these compounds to moisture,[39] a small amount of acid had developed within the samples and they were recrystallized from ether. This recrystallization removed the acid but, if anything, the 1-adamantanol was concentrated. However, control experiments showed the 1-adamantanol concentration to remain unchanged during reaction and these samples, all containing less than 10% 1-adamantanol, were acceptable for use in the product studies. In one instance, for a reaction of 1-adamantyl *p*-chlorobenzenesulfonate, a freshly prepared analytically pure sample was used and only 1.1% 1-adamantanol was detected within the products; this gives an approximate measure of the extent of interaction with moisture during preparation of a reaction mixture. Control experiments showed that 1-adamantyl azide and 1-(1-adamantyl)-5-methyltetrazole do not interconvert under the experimental conditions.

The glpc analysis was carried out using a Varian Aerograph Series 1700 instrument, equipped with a thermal conductivity detector and a Sargent Recorder, Model SRG (with disc integrator). A 2 ft × 0.25 in. column packed with 30% SE-30 on 80 mesh Chromosorb W was maintained initially at 85° and the instrument was temperature programmed so that the column temperature had risen to no higher than 225° at the time of elution of the tetrazole (at higher temperatures decomposition was observed).

Use of authentic samples showed that the plausible components (in order of elution) were as follows: acetonitrile, 1-adamantanol, 1-adamantyl azide, *N*-(1-adamantyl)acetamide[18,40] (from possible capture of the solvolysis product by adventitious moisture), unreacted 1-adamantyl arenesulfonate, and 1-(1-adamantyl)-5-methyltetrazole. Good peak separation was obtained under the experimental conditions. After completion of reaction with excess tetraethylammonium azide, only 1-adamantanol (concentration unchanged from that present originally), 1-adamantyl azide, and 1-(1-adamantyl)-5-methyltetrazole were detected, in the proportions reported in Table IV. In calculating the competition factors, the initial concentration of 1-adamantyl arenesulfonate entered into the equation[24] was corrected for the 1-adamantanol impurity.

In a few cases the crude reaction product was isolated by parti-

Table V

A. Temperature, 39.6°; 2-ml Aliquots; [$C_{10}H_{15}OTs$], 0.100 *M*; [NEt_4N_3], 0.080 *M*; Titers, Milliliters of 0.0198 *M* Methanolic HCl

Time, sec	0	7200	10,800	15,900	21,400	26,000
Titer	7.81	6.76	6.40	5.71	5.08	4.65
$10^5 k_1$, sec^{-1}		1.60	1.46	1.54	1.56	1.52
Time, sec	34,900	40,800	49,600			
Titer	3.74	3.24	2.52			
$10^5 k_1$, sec^{-1}	1.57	1.57	1.60			

B. Temperature, 39.6°; 2-ml Aliquots; [$C_{10}H_{15}OTs$], 0.100 *M*; [NEt_4N_3], 0.080 *M*; [NEt_4ClO_4], 0.040 *M*; Titers, Milliliters of 0.0198 *M* Methanolic HCl

Time, sec	0	7200	10,800	14,900	20,400
Titer	7.76	6.72	6.22	5.68	4.99
$10^5 k_1$, sec^{-1}		1.60	1.62	1.64	1.67
Time, sec	25,700	35,600	39,800	48,500	
Titer	4.47	3.55	3.03	2.27	
$10^5 k_1$, sec^{-1}	1.64	1.67	1.70	1.74	

C. Temperature, 25.0°; 2-ml Aliquots; [$C_{10}H_{15}OSO_2C_6H_4$-*p*-NO_2], 0.100 *M*; [NEt_4N_3], 0.080 *M*; Titers, Milliliters of 0.0156 *M* Methanolic HCl

Time, sec	0	169	390	575	777	1012
Titer	9.58	8.95	8.15	7.59	6.97	6.23
$10^5 k_1$, sec^{-1}		31.7	32.0	31.0	31.1	31.8
Time, sec	1212	1423	1607			
Titer	5.84	5.28	4.92			
$10^5 k_1$, sec^{-1}	32.3	32.5	31.8			

tion between water and ether and evaporation of the ether. The relatively small amounts of 1-adamantyl azide (and 1-adamantanol?) could be removed by sublimation under reduced pressure at 40°, to leave a residue of 1-(1-adamantyl)-5-methyltetrazole.[19] Alternatively, the crude reaction product could be separated by chromatography on a column containing neutral alumina. The 1-adamantyl azide[16,19] was eluted using benzene, followed by elution of the tetrazole[19] using 50:50 hexane–benzene or chloroform.

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References and Notes

(1) Abstracted, in part, from the Ph.D. Thesis of C.-B. K., Northern Illinois University, June 1973.
(2) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969.
(3) D. J. Raber, J. M. Harris, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 4821 (1971).
(4) R. A. Sneen, J. V. Carter, and P. S. Kay, *J. Amer. Chem. Soc.*, **88**, 2594 (1966).
(5) H. Weiner and R. A. Sneen, *J. Amer. Chem. Soc.*, **87**, 287, 292 (1965).
(6) C. D. Ritchie, *Accounts Chem. Res.*, **5**, 348 (1972).
(7) H. L. Goering and J. F. Levy, *J. Amer. Chem. Soc.*, **86**, 120 (1964).
(8) S. Winstein, B. Appel, R. Baker, and A. Diaz, *Chem. Soc., Spec. Publ.*, **No. 19**, 109 (1965).
(9) J. M. Harris, J. F. Fagan, F. A. Walden, and D. C. Clark, *Tetrahedron Lett.*, 3023 (1972).
(10) J. M. Harris, A. Becker, D. C. Clark, J. F. Fagan, and S. L. Kennan, *Tetrahedron Lett.*, 3813 (1973).
(11) C. D. Ritchie, *J. Amer. Chem. Soc.*, **93**, 7324 (1971).
(12) P. v. R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *J. Amer. Chem. Soc.*, **92**, 2542 (1970).
(13) D. J. Raber and J. M. Harris, *J. Chem. Educ.*, **49**, 60 (1972).
(14) D. J. Raber, R. C. Bingham, J. M. Harris, J. L. Fry, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 5977 (1970).
(15) V. J. Shiner, Jr. and R. D. Fisher, *J. Amer. Chem. Soc.*, **93**, 2553 (1971).
(16) T. Sasaki, S. Eguchi, and T. Toru, *Bull. Soc. Chem. Jap.*, **42**, 3613 (1969).
(17) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, **67**, 247 (1967).
(18) D. N. Kevill and F. L. Weitl, *J. Amer. Chem. Soc.*, **90**, 6416 (1968).
(19) D. N. Kevill and F. L. Weitl, *J. Org. Chem.*, **35**, 2526 (1970).
(20) L. A. Lee, R. Evans, and J. W. Wheeler, *J. Org. Chem.*, **37**, 343 (1972).
(21) (a) W. A. Mueller, Ph.D. Thesis, University of London, Sept 1959; (b) Y. Pocker, W. A. Mueller, F. Naso, and G. Tocchi, *J. Amer. Chem. Soc.*, **86**, 5011 (1964).
(22) D. N. Kevill, K. C. Kolwyck, D. M. Shold, and C.-B. Kim, *J. Amer. Chem. Soc.*, **95**, 6022 (1973).
(23) J. M. Harris, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 5729 (1970).
(24) The required integrated form of the relationship has been derived previously and is reported in ref **4** (footnote 4).
(25) H. M. R. Hoffmann, *J. Chem. Soc.*, 6753 (1965).
(26) D. N. Kevill and R. F. Sutthoff, *J. Chem. Soc. B*, 366 (1969).
(27) B. Gutbezahl and E. Grunwald, *J. Amer. Chem. Soc.*, **75**, 559 (1953).
(28) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).
(29) This is also apparent from the results reported earlier.[3] Competition factors of 2.5 and 1.7 were obtained for 1-adamantyl bromide and 2-adamantyl *p*-toluenesulfonate in 80% ethanol containing azide ion, when competition between water and azide ion was considered. Consideration of competition between the ethanol of the solvent and the azide ion leads to corresponding values of 2.4 and 4.7. Taken at their face value these latter values are in conflict with the ones reported earlier for the azide ion and water competition and they suggest the 2-adamantyl carbonium ion to be more stable than the 1-adamantyl carbonium ion. The valid conclusion is, of course, that one cannot directly compare, in this solvent, product studies obtained using bromides with those using *p*-toluenesulfonates.[10] Accordingly, even if one accepts that competition factors with azide ion in 80% ethanol at 75° can be related to those in 80% acetone at 25°, the inclusion of product-partitioning data for bromides and, especially, *p*-toluenesulfonates on a stability–selectivity plot for chlorides[3] is, at best, a very approximate procedure.
(30) For example, acetonitrile has been a suitable solvent for studies of hydrolyses[31] and methanolyses[32] of acyl halides.
(31) M. L. Bender and M. C. Chen, *J. Amer. Chem. Soc.*, **85**, 30 (1963).
(32) D. N. Kevill and F. D. Foss, *J. Amer. Chem. Soc.*, **91**, 5054 (1969).
(33) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
(34) G. Atkinson and S. K. Kor, *J. Phys. Chem.*, **71**, 673 (1967).
(35) Even if attack was at either an intimate ion-pair or free carbonium ion stage, solvation both of the carbonium ion and, in protic solvents, of the azide ion would remove the statistical requirements that highly reactive carbonium ions (which have the low competition factors) give values in excess of unity.[3] Such carbonium ions would tend to react either with their own solvating molecules or with those protecting the azide ion, which could render general base catalysis to their attack.[6]
(36) D. N. Kevill and J. E. Dorsey, *J. Org. Chem.*, **34**, 1985 (1969).
(37) D. N. Kevill, K. C. Kolwyck, and F. L. Weitl, *J. Amer. Chem. Soc.*, **92**, 7300 (1970).
(38) H. Wolff, *Org. React.*, **3**, 307 (1947).
(39) P. v. R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83**, 2700 (1961).
(40) H. Stetter, M. Schwarz, and A. Hirschhorn, *Ber.*, **92**, 1629 (1959).

Hofmann Elimination and Stevens Rearrangement with *N,N,N*-Trimethyl-3-homoadamantylammonium Hydroxide.[1] Evidence for 3-Homoadamantene

Benjamin L. Adams[2,3] and Peter Kovacic*

Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

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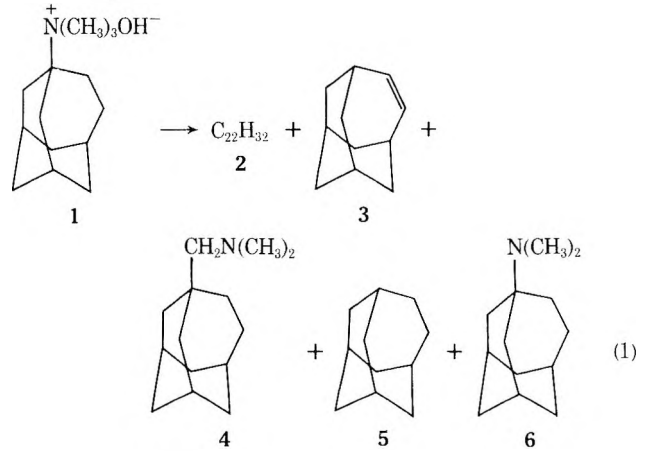
Pyrolysis of *N,N,N*-trimethyl-3-homoadamantylammonium hydroxide provided four dimers of bridgehead homoadamantene (10%), 4-homoadamantene (0.3%), *N,N*-dimethyl-3-aminomethylhomoadamantane (43%), homoadamantane (5%), and *N,N*-dimethyl-3-aminohomoadamantane (11%). The cyclobutane structure in the dimers was established by laser Raman and mass spectral data. Additional evidence for 3-homoadamantene was obtained from trapping by 1,3-diphenylisobenzofuran. *N,N*-Dimethyl-3-aminomethylhomoadamantane was formed by the unusual migration of a tertiary group during Stevens rearrangement.

Considerable interest has been shown recently in delineating the limits of Bredt's rule[4-8] and in finding a basis for predicting the degree of stability of bridgehead double bonds. Hofmann elimination[4] and bisdehalogenation of vicinal dihalides[5] have been used to produce highly strained olefins which, in many cases, have been isolated as Diels–Alder adducts or [2 + 2] dimers. Most of the prior work has been done in the bicyclic series. The isolation of dimer has been cited[5a,b] as evidence for the existence of adamantene. This report presents evidence for the formation of 3-homoadamantene as an intermediate in the pyrolysis of *N,N,N*-trimethyl-3-homoadamantylammonium hydroxide (1).

In contrast to Hofmann elimination[4] in less strained systems, a Stevens rearrangement product, arising from unusual migration of a tertiary group, was found in moderate yield. Stevens rearrangement[9] usually occurs in the absence of a β hydrogen, the presence of a rather acidic α hydrogen, or the involvement of a migrating group capable of stabilizing a negative charge or radical.

Results and Discussion

N,N,N-Trimethyl-3-homoadamantylammonium hydroxide (1) was prepared from the known amine[10] by standard techniques. Decomposition at 140–175° (1 mm) provided a mixture of dimers of 3-homoadamantene (**2**, 10%), 4-homoadamantene[11,12] (**3**, 0.3%), *N,N*-dimethyl-3-aminomethylhomoadamantane (**4**, 43%), homoadamantane[11] (**5**, 5%), and *N,N*-dimethyl-3-aminohomoadamantane[10] (**6**, 11%), eq 1.

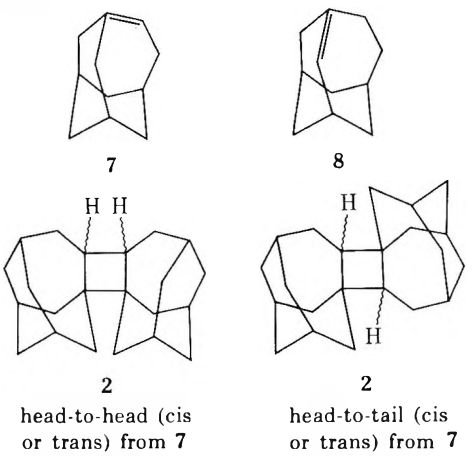


(1)

Reaction conditions are of particular importance in determining the pathway which is followed. If the procedure entails heating from room temperature, mostly parent amine is obtained. Apparently, much of the quaternary salt is destroyed by SN2 attack[13] of hydroxide ion before rearrangement or elimination can take place.

The dimer mixture **2** was isolated as a white solid which had sublimed at the higher temperatures to cooler portions of the pyrolysis flask. Gas chromatography revealed four peaks [a (29%), b (8%), c (3%), and d (60%)]. Components **2a** and **2d** were identified as dimers of 3-homoadamantene by ir, nmr, laser Raman, and mass spectral data, elemental analysis, and comparison to dimers from Cope elimination with *N,N*-dimethyl-3-aminohomoadamantane *N*-oxide[1] and from rearrangement of 1-adamantylcarbene.[8] No report of the use of laser Raman spectroscopy for identification of this type of structure has been made prior to the communications from our[1] and Schleyer's[8] laboratories. By comparison to previous studies of substituted cyclobutanes[14,15] as well as to laser Raman spectra of homoadamantane, adamantane, and adamantene dimer,[16] we have assigned[17,18] bands to ring deformations and ring puckering in the cyclobutane structure of **2**. The low-frequency Raman lines are particulary useful since similar bands were observed[14] in other systems and assigned to ring puckering.

The quaternary hydroxide **1** can eliminate to give, theoretically, two olefins, **7** and **8**. These alkenes could then undergo cycloaddition resulting in a total of 16 geometric isomers. Since only four different dimers were observed by glpc analysis and three of these (**2a, 2b,** and **2d**) correspond to dimers isolated from the rearrangement of 1-adamantylcarbene[8] which can give only **7**, we conclude that decomposition of **1** proceeds essentially exclusively to **7**. Alternatively, **8**, if formed, rearranges quickly to **7** *via* 1,3-hydride shift.[19] Each of the isomers, **2a, 2b,** and **2d,** gave the same glpc retention time as the corresponding dimer from 1-adamantylcarbene rearrangement,[8] and **2a** and **2d** were identical with their counterparts from 1-adamantylcarbene ac-



cording to laser Raman spectral data. On the basis of the available spectral data, we are unable to assign definite structures to the individual dimers. However, we have tentatively suggested that major component d has the "head-to-head trans" geometry and that a is the "head-to-tail cis" isomer.[17,18,20]

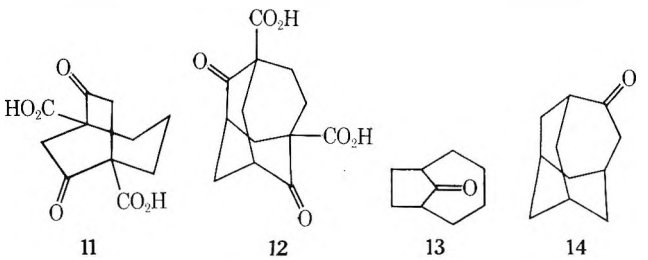
The formation of olefin **3** is at variance with results[4] from the bicyclic systems, since this type of product was not observed in the earlier work. Wiseman and Chong[4c] were able to isolate bicyclo[3.2.2]non-1-ene (**9**) and bicyclo-[3.2.2]non-1(7)-ene (**10**) at Dry Ice temperatures using Hofmann elimination at the bridgehead. These olefins dimerized fairly rapidly on warming to room temperature, but did not isomerize to the more stable 2 isomer. Since **7** is more reactive than **9** and **10** and of higher molecular weight, it is not able to escape from the reaction mixture before dimerization or isomerization.

9 **10**

There are at least three plausible routes which could account for the presence of **3**. The intermediate bridgehead olefin **7** may undergo base-catalyzed isomerization or 1,3-hydride shift.[19] A less appealing possibility is that 1,3-elimination gives rise to 3,5-dehydrohomoadamantane, followed by 1,2-hydride shift. Since 1,3-dehydroadamantane[21] is an isolable, though reactive, compound, it is likely that some of the homoadamantyl analog would, if formed, survive the reaction conditions.

The generation of bridgehead homoadamantene **7** appears to fit Wiseman's[4a] generalization that the strain of a bridgehead double bond is closely related to the strain of the corresponding *trans*-cycloalkene. In this case the double bond is trans in a seven-membered ring and should have roughly the same amount of strain as *trans*-cycloheptene[22] and bridgehead *trans*-cycloheptenes in the bicyclic series.[4c,d] We have found no example of a strained alkene of this ring size in a tricyclic system. The additional bridge in the homoadamantyl skeleton produces a more rigid framework which would likely increase the strain of a double bond at the bridgehead. This appears to be the case with **7**.

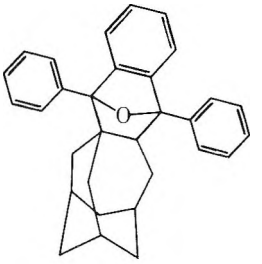
A comparison of the keto acids **11** and **12** supports the thesis that **7** possesses somewhat greater strain than the singly bridged *trans*-cycloheptenes **9** and **10**. The mechanism[23] of decarboxylation is commonly accepted as involving an enol intermediate. Although both compounds would form a bridgehead enol trans in a seven-membered ring, **11** undergoes decarboxylation[24] at 218°, whereas **12** decomposes at a somewhat higher temperature, 280°.[25] A partial exchange of the bridgehead proton for deuterium on treatment with sodium methoxide in D_2O at reflux was found for bicyclo[4.2.1]nonan-9-one[26] (**13**). No incorporation[27] of



11 **12** **13** **14**

deuterium was observed at the bridgehead of 4-homoadamantanone on exposure to sodium *tert*-butoxide–*tert*-butyl alcohol-*O-d*, even though Schleyer and coworkers[27] noted from models that the corresponding enol is not impossibly strained. Therefore, with these differences in mind, Wiseman's modification of Bredt's rule also applies in the present case.

Several experiments were undertaken in order to trap the intermediate bridgehead olefin during pyrolysis. The quaternary hydroxide **1** was decomposed in the presence of 1,3-diphenylisobenzofuran (DPIBF), a reagent that has been successfully employed in previous, related work.[4,22] A 10% yield of the Diels–Alder adduct **15** was isolated from

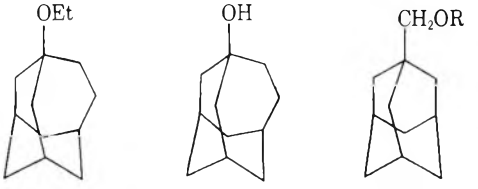


15

the residue in the pyrolysis flask by column chromatography on alumina, followed by purification *via* preparative thin layer chromatography on silica gel (no more than 10% of isomeric adduct could be present). Since the melting range is small, the trapped product is probably a single isomer. This evidence further supports the contention that **7** is the preferred product from elimination.

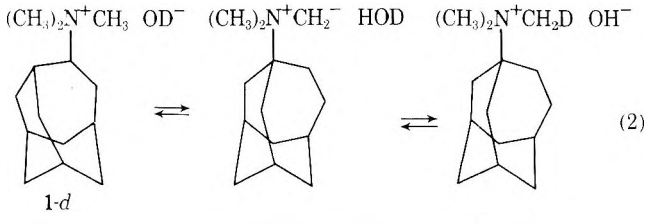
Ethanol and water were also explored as trapping agents by sealing the reactants in a glass tube which was immersed in an oil bath at 145–150° for 1–2 hr. Additions[4a,c,6,7a] of weak Brønsted acids to bridgehead olefins have been observed in bicyclic systems. Bicyclo[3.3.1]non-1-ene,[4a,6] **9**,[4c] and **10**[4c] all add acetic acid or ethanol in the presence of traces of acid. Adamantene[7a] was proposed as an intermediate in a recent study on the basis of presumed capture by methanol and methanol-*O-d*. Reaction in our case afforded the ether, 3-ethoxyhomoadamantane[28,29] (**16**, 8%), plus 3-hydroxyhomoadamantane[30] (**17**, 8%) from involvement of water present in the quaternary hydroxide or generated during reaction, in addition to **4** (62%), **5** (2%), and **6** (1%). No dimers or 4-homoadamantene (**3**) were detected in the product mixture; note that the combined yield of **16** and **17** approximates the yield of dimer from the standard system. Compound **16** was identified by ir and nmr spectra, as well as by comparison to authentic material prepared by reaction of the sodium salt of **17** with ethyl iodide. The absence of dimer **2** and olefin **3** suggests that 3-homoadamantene was successfully trapped before occurrence of dimerization or isomerization. On the other hand, **16** and **17** may arise from solvolysis. In this type of situation, one might expect some rearrangement to the thermodynamically favored[29] adamantylcarbinyl structure (alcohol **18** or ether **19**), none of which was detected. It might be that solvolyzed material exists as a tight ion–molecule pair which is not favorably disposed toward rearrangement.

Thermolysis of the quaternary deuteroxide **1**-*d* in ethanol-*O-d* did not provide straightforward corroboration of Brønsted acid addition to **7**. No C–D stretching vibration was observed in the ir spectra of **16** and **17**, and the mass



16 **17** **18**, R = H
19, R = Et

spectrum indicated an increase of only a few per cent for the P + 1 peak. Amines **4** and **6** in the product contained 1–2 atoms of deuterium per molecule on the basis of ir and mass spectral data. A possible rationalization of the results is that proton–deuterium exchange with the methyl groups of 1-*d*, eq 2, takes place rapidly compared to elimination, giving mostly EtOH, rather than EtOD, eq 3, in the vicinity of the forming bridgehead olefin. However, the solvolytic mechanism appears more in keeping with these observations.



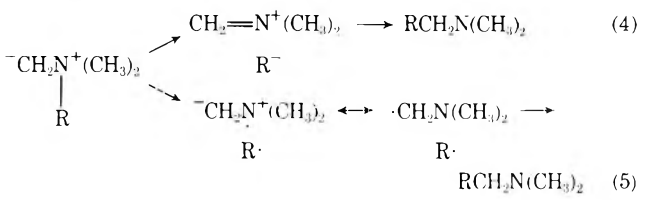
1-*d* (2)

$$OH^- + EtOD \rightleftharpoons HOD + EtO^- \rightleftharpoons OD^- + EtOH \quad (3)$$

Precise details of the elimination mechanism for quaternary salt **1** were not investigated. The impossibility of trans elimination and steric blocking of β hydrogens by the NMe_3^+ group may favor an $E_{\alpha'-\beta}$ process as stated by prior investigators.[13] Evidence for the presence of ylide, involved in the $E_{\alpha'-\beta}$ process, was provided by decomposition of the quaternary deuteroxide **1**-*d*, which yielded deuterated amines **4** and **6**.

The Stevens rearrangement product, **4**, was identified by comparison to authentic material prepared by independent synthesis. 3-Homoadamantanecarboxamide[10] was reduced with $LiAlH_4$ to give 3-aminomethylhomoadamantane. Methylation with formaldehyde and formic acid gave tertiary amine **4**, identical with the product from pyrolysis. Very little has been reported[31] on this type of rearrangement for simple tetraalkylammonium systems, with the exception of the tetramethyl type. Our results represent an unusual Stevens rearrangement, since we have found no prior examples[32] involving migration of a secondary or tertiary group.

Two mechanistic possibilities[9,33,34] have been advanced for the nature of the migrating group in this rearrangement, namely carbanion and radical. Base can remove a proton from a methyl group to give an ylide. Rearrangement then occurs by dissociation to either an ion pair, eq 4, or a radical pair, eq 5, followed by recombination. At least



(4) (5)

for certain systems, the radical pathway appears to be favored currently.[32,34] Migration of the homoadamantyl group is in keeping with a radical mechanism, although relief of strain may play an important role. A significant amount of crowding appears to be present in **1** owing to the two adjacent quaternary atoms (bridgehead carbon and nitrogen). It is pertinent that the analogous 1-*tert*-butyladamantane[35] has been made only with great difficulty. Pine and coworkers[33] found that the similar rearrangement in the neopentyl system was greatly influenced by steric requirements.

Formation of **4** resembles the generation of neopentane as a by-product in the Stevens rearrangement of *N,N,N*-trimethylneopentylammonium iodide.[33] Apparently the reactive intermediates can separate to some extent with subsequent abstraction of a proton[33] or hydrogen atom. Although bishomoadamantyl, theoretically possible *via* combination of the radical intermediates, was not detected, this finding does not rule out the homolytic mechanism, since the intermediates may be present in such low concentration that dimerization cannot compete with hydrogen abstraction.

In contrast to the present results, pyrolysis[4] of the bridgehead trimethylbicyclononyl and bicyclooctylammonium hydroxides afforded only the corresponding strained olefin, or its dimer, and the parent amine. No Stevens rearrangement product, isomerized olefin, or parent hydrocarbon was reported. These differences may be rationalized by the apparently greater ease of elimination in the bicyclic systems.

A comparison of the results from the adamantyl[32] and homoadamantyl systems gives an indication of the relative strain of adamantene and 3-homoadamantene and also shows the limitation of the Hofmann elimination method for producing strained olefins. In the decomposition of **1**, elimination and rearrangement occur at competing rates. For the adamantyl system, however, elimination is so unfavorable that Stevens rearrangement and SN2 attack by hydroxide ion account for all observed products. Therefore, 3-homoadamantene would appear to be nearing the limit of the type of *trans*-cycloalkene which can be formed by Hofmann elimination.

Experimental Section

Ir spectra were obtained with a Perkin-Elmer 137 spectrophotometer (calibrated with the 1601.8-cm^{-1} band of polystyrene). Varian T-60 and HA-100 instruments were used to obtain nmr data, which are reported in parts per million (δ) (in CCl_4) relative to tetramethylsilane as internal standard. Laser Raman spectra were obtained from a Ramex Spex 1401 spectrophotometer, measured from the green excitation line (19,436 cm^{-1}). Microanalyses were performed by Baron Consulting Co., Orange, Conn., and Dr. R. E. White. Some of the mass spectral data were provided by Drs. Michael Kurz and Robert D. Fisher. Glpc analyses were conducted on Varian Aerograph 1800, 1700, and 90P instruments with the indicated columns: (I) 15% Carbowax 20M on Chromosorb W (45/60 mesh), 10 ft × 0.25 in., copper; (II) 15% Carbowax 20M and 5% NaOH on Chromosorb P (30/60 mesh), 10 ft × 0.25 in., copper; (III) 15% Carbowax 20M on Chromosorb W (45/60 mesh), 6 ft × 0.25 in., copper; (IV) 5% Carbowax 20M on Chromosorb W (45/60 mesh), 5 ft × 0.25 in., copper. Melting points (uncorrected) were obtained with a Thomas-Hoover capillary melting point apparatus.

***N,N,N*-Trimethyl-3-homoadamantylammonium Iodide.** Methyl iodide (5.9 g, 0.042 mol) was added to *N,N*-dimethyl-3-aminohomoadamantane[10] (**6**, 4 g, 0.021 mol) in 50 ml of absolute ether. A white precipitate formed immediately. After the mixture was allowed to stand overnight, the salt was filtered and dried. Recrystallization from ethanol–ether gave 4.6 g (66% yield), mp 282–283° dec.

Anal. Calcd for $C_{14}H_{26}NI$: C, 50.15; H, 7.82. Found: C, 50.02; H, 7.55.

***N,N,N*-Trimethyl-3-homoadamantylammonium Hydroxide (1).** Silver oxide (5.6 g , 0.024 mol) was added to a mixture of the ammonium iodide (5.6 g, 0.017 mol), 30 ml of distilled water, and 40 ml of ethanol. The mixture was stirred for 5 hr at room temperature and then was filtered to remove silver salts. Evaporation of solvent and drying under vacuum overnight gave 4.4 g (3.8 g, theory) of a gray-white solid which was extremely hygroscopic. Elemental analysis indicated that the crude material was approximately 74% **1**.

Pyrolysis of 1. In a typical run, 1.42 g (0.0045 mol) of **1** was placed in a 15-ml, round-bottomed flask connected through a short-path distillation head to a 10-ml receiver cooled in an acetone–Dry Ice bath. Vacuum (1 mm) was applied while the oil bath was preheated to 140°. The pyrolysis flask was immersed in the bath and heating was continued to 180° over a period of 1.5 hr. The distillate (0.86 g) was taken up in ether and extracted with 2 *N* HCl. The ether layer was dried and evaporated to give neutral products (0.11 g). Glpc analysis on column I indicated that the

neutral fraction was 35% **5**,[11] mp 257–258° (sealed tube) (5.4% yield), 2% **3**,[11,12] mp 237–238° (sealed tube) (0.3% yield), and some dimeric material (<1%).

The acid layer was evaporated to approximately 1 ml and added to 50 ml of 20% NaOH. The mixture was extracted with ether. The ether solution was dried and evaporated to give 0.68 g of basic products. Glpc analysis on column II indicated 60% of **4** (43% yield) and 14% of **6**[10] (11% yield).

A white solid (0.067 g) sublimed at 180° under vacuum from the reaction mixture into the distillation head. Glpc analysis on column IV showed it to be a mixture of four components, **2a** (29%), **2b** (8%), **2c** (3%), and **2d** (60%).

Samples of **2a** and **2d** for spectra and microanalysis were collected from column III. Separation was effected on a 6-ft OV-1 column attached to a mass spectrometer.

2a: mp 252–256°; nmr δ 1.3–2.8 (broad m); ir (KBr) 2820, 2600 (w), 1445, 928, 810 (w), 785 cm^{-1} (w); mass spectrum, parent ion, *m/e* 296.

Anal. Calcd for $C_{22}H_{32}$: C, 89.12; H, 10.88. Found: C, 88.89; H, 10.78.

2b: mass spectrum, parent ion, *m/e* 296.

2c: mass spectrum, parent ion, *m/e* 296.

2d: mp 195–200°; nmr δ 1.3–2.8 (broad m); ir (KBr) 2810, 2610 (w), 1440, 930, 802 (w), 783 cm^{-1} (w); mass spectrum, parent ion, *m/e* 296.

Anal. Calcd for $C_{22}H_{32}$: C, 89.12; H, 10.88. Found: C, 88.91; H, 10.81.

3-Aminomethylhomoadamantane.[10] $LiAlH_4$ (1.5 g, 0.039 mol) was suspended in 40 ml of dry tetrahydrofuran. After 3-homoadamantanecarboxamide[10] (2 g, 0.011 mol) in 20 ml of dry tetrahydrofuran was added slowly, the mixture was refluxed for 72 hr and then was cooled. Water (1.5 ml), 10% NaOH (1.5 ml), and water (3 ml) were carefully added. The mixture was filtered and the precipitate was washed with ether. The combined ether layer was dried and evaporated to give crude amine (1.7 g).

***N,N*-Dimethyl-3-aminomethylhomoadamantane (4).** The crude 3-aminomethylhomoadamantane from above (1.7 g) was added to 97% formic acid (10 ml) and formaldehyde (10 g). The solution was heated at 95° for 7 hr and then was cooled. After 10 ml of 4 *N* HCl was added, the solution was evaporated to approximately 5 ml. The concentrated solution was added to 60 ml of ice-cold, 20% NaOH and the mixture was extracted with ether. The ether solution was dried and evaporated to give a reasonably pure (95%) sample of 4 (0.95 g). Glpc collection on column II provided pure **4**: ir (neat) 1430, 1250, 1140, 1027, and 835 cm^{-1}; nmr δ 2.23 (d, 8 H), 2.1–1.3 (m, 17 H).

Anal. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 12.15; N, 6.76. Found: C, 81.22; H, 12.26; N, 6.59.

Homoadamantane (5). 4-Homoadamantene[11,12] (**3**, 57 mg) and Pd/C (22 mg) were added to 8 ml of absolute ethanol in a Parr apparatus. After the mixture was shaken with hydrogen for 20 hr, the catalyst was filtered and the filtrate was evaporated to give **5** (19 mg). Glpc collection on column I provided a pure sample for comparison to the corresponding product from pyrolysis.

Pyrolysis of 1 with 1,3-Diphenylisobenzofuran (DPIBF). The quaternary hydroxide **1** (2 g, 6.7 mmol) and DPIBF (2 g, 9.3 mmol) were placed in a 25-ml, round-bottomed flask connected through a short-path distillation head to a 10-ml receiver cooled in an acetone–Dry Ice bath. Vacuum (15 mm) was applied and the flask was immersed in an oil bath at 140° for 1.5 hr. At this time the vacuum was adjusted to 0.2 mm in order to remove any volatile products present in the reaction flask. After the apparatus had cooled, the residue in the pyrolysis flask was taken up in 100 ml of benzene. Maleic anhydride was added to decompose excess DPIBF. After 50% NaOH in an equal volume of methanol (25 ml) was added to the benzene, the mixture was refluxed for 30 min. The organic layer was separated, washed with water, dried, and evaporated to yield 0.83 g of yellow solid. Column chromatography on alumina (10 cm, elution with benzene) yielded 0.41 g of a yellow solid in the third fraction (25 ml). This material contained four impurities comprising about 20% of the mixture. Preparative-scale tlc with silica gel–benzene, followed by washing with ether, provided pure **15** (10% yield):[36] mp 187–190°; ir (KBr) 3000, 2895, 1595, 1490, 1445, 995, 785, 748, 701 cm^{-1}; nmr[37] δ 6.95–7.80 (m, 14 H), 1.0–2.8 (m, 16 H); mass spectrum, parent ion, *m/e* 418.

Decomposition of 1 in Ethanol. A homogeneous solution of the vacuum-dried quaternary hydroxide [0.089 g consisting of 0.068 g (3 mmol) of **1** and 0.021 g (1.2 mmol) of H_2O] in 0.27 g (5.7 mmol) of absolute ethanol was heated in a sealed tube for 2 hr at 140–145°. The resultant solution was taken up in ether, followed by extraction with 1 *N* HCl. Analysis of the ether layer for neutral products by glpc on column I indicated the presence of **5** (1.6%), **16** (7.5%), and **17** (7.8%).

After the aqueous acid fraction was added to 25% NaOH, extraction was effected with ether. The ether layer was dried and analyzed by glpc on column II. Basic products **4** (62%) and **6** (1.2%) were identified.

The product distribution was found to be sensitive to the amount of water present, with increased quantities providing substantially more **17** and **6**.

3-Ethoxyhomoadamantane[28,29] **(16).** Sodium (0.30 g, 13 mmol) was added to 3-hydroxyhomoadamantane[30] (**17**, 2.0 g, 12 mmol) in 25 ml of tetrahydrofuran. The mixture was refluxed until all of the sodium had reacted, and a fine, white powder (alkoxide) was present. After ethyl iodide (3.5 g, 0.024 mol) was added, the mixture was refluxed overnight. Glpc analysis on column I indicated a 10% yield of **16**: ir (neat) 2900, 1440, 1375, 1150, 1105, 1070, 1015, and 977 cm^{-1}; nmr δ 3.39 (q, J = 7 Hz, 2 H), 2.1–1.4 (m, 17 H), 1.04 (t, J = 7 Hz, 3 H).

N,N,N*-Trimethyl-3-homoadamantylammonium Deuterioxide.** The deuterioxide (**1-*d) was prepared as described for **1**, by use of ethanol-*O*-*d* and D_2O in place of ethanol and water.

Pyrolysis of 1-*d* in Ethanol-*O*-*d*. Reaction was carried out as described for nondeuterated material. The ir spectra of **16-*d*** and **17-*d*** showed no absorption in the region of 1900–2200 cm^{-1}. The mass spectral parent peaks occurred at *m/e* 167 and 195 for **16-*d*** and **17-*d***, with increases in P + 1 peaks of 1.7 and 1.3%, respectively.

Acknowledgment. We thank the National Science Foundation and the Graduate School, University of Wisconsin—Milwaukee, for support of this work, Professor K. L. Watters for assistance with the laser Raman spectra, Professors Michael Kurz and Robert Fisher for mass spectral data, Dr. R. E. White for elemental analyses and helpful discussions, Professor P. v. R. Schleyer for making available his unpublished work, and the referees for helpful comments.

Registry No.—**1**, 50782-20-2; **2**, head-to-head cis, 50782-17-7; **2**, head-to-head trans, 50898-71-0; **2**, head-to-tail cis, 52208-36-3; **2**, head-to-tail trans, 50898-72-1; **3**, 24669-57-6; **4**, 50782-21-3; **5**, 281-46-9; **6**, 50782-22-4; **15**, 52175-61-8; **16**, 14504-82-6; **17**, 14504-80-4; *N,N,N*-trimethyl-3-homoadamantylammonium iodide, 52175-62-9; 3-aminomethylhomoadamantane, 52175-63-0.

References and Notes

(1) Paper IX, "Adamantanes and Related Compounds." Preliminary communication: B. L. Adams and P. Kovacic, *J. Amer. Chem. Soc.*, **95**, 8206 (1973).
(2) Graduate School Fellow, 1973–1974.
(3) Taken in part from the Ph.D. Thesis of B. L. A., 1974.
(4) (a) J. R. Wiseman and W. A. Pletcher, *J. Amer. Chem. Soc.*, **92**, 956 (1970); (b) J. R. Wiseman, H. F. Chan, and C. J. Ahola, *ibid.*, **91**, 2812 (1969); (c) J. R. Wiseman and J. A. Chong, *ibid.*, **91**, 7775 (1969); (d) J. A. Chong and J. R. Wiseman, *ibid.*, **94**, 8627 (1972).
(5) (a) D. Grant, M. A. McKervey, J. J. Rooney, N. G. Samman, and G. Step, *J. Chem. Soc., Chem. Commun.*, 1186 (1972); (b) D. Lenoir, *Tetrahedron Lett.*, 4049 (1972); (c) R. Keese and E.-P. Krebs, *Angew. Chem., Int. Ed. Engl.*, **10**, 262 (1971); (d) *ibid.*, **11**, 518 (1972).
(6) J. A. Marshall and H. Faubl, *J. Amer. Chem. Soc.*, **92**, 948 (1970).
(7) (a) J. E. Gano and L. Eizenberg, *J. Amer. Chem. Soc.*, **95**, 972 (1973); (b) A. H. Alberts, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 3047 (1973); (c) H. H. Grootveld, C. Blomberg, and F. Bickelhaupt, *J. Chem. Soc., Chem. Commun.*, 542 (1973); (d) G. L. Buchanan and G. Jamieson, *Tetrahedron*, **28**, 1123, 1129 (1972); (e) S. F. Campbell, R. Stephens, and J. C. Tatlow, *ibid.*, **21**, 2997 (1965); (f) A. D. Wolf and M. Jones, Jr., *J. Amer. Chem. Soc.*, **95**, 8209 (1973).
(8) M. Farcasiu, D. Farcasiu, R. T. Conlin, M. Jones, Jr., and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **95**, 8207 (1973).
(9) S. H. Pine, *Org. React.*, **18**, 403 (1970).
(10) E. I. du Pont de Nemours and Co., Netherlands Appl. 6,404,755 (1964); *Chem. Abstr.*, **63**, 6887 (1965).
(11) R. M. Black and G. B. Gill, *J. Chem. Soc. C*, 671 (1970); Z. Majerski, S. H. Liggero, and P. v. R. Schleyer, *Chem. Commun.*, 949 (1970).
(12) We thank Dr. G. B. Gill and Dr. Z. Majerski for samples of 4-homoadamantene.
(13) A. C. Cope and E. R. Trumbull, *Org. React.*, **11**, 317 (1960).
(14) J. R. Durig, W. H. Green, and N. C. Hammond, *J. Phys. Chem.*, **70**, 1989 (1966).
(15) D. N. Harpp and C. Heitner, *J. Org. Chem.*, **35**, 3256 (1970).
(16) We thank Dr. D. Lenoir and Dr. M. A. McKervey for samples of adamantene dimer.
(17) B. L. Adams and P. Kovacic, *J. Amer. Chem. Soc.*, in press.

(18) A more extensive treatment is presented in ref 17.
(19) H. Gerlach, T. T. Huong, and W. Müller, *J. Chem. Soc., Chem. Commun.*, 1215 (1972).
(20) P. v. R. Schleyer, personal communication.
(21) R. E. Pincock, J. Schmidt, W. B. Scott, and E. J. Torupka, *Can J. Chem.*, **50**, 3958 (1972).
(22) E. J. Corey, F. A. Carey, and R. A. E. Winter, *J. Amer. Chem. Soc.*, **87**, 934 (1965).
(23) F. H. Westheimer and W. A. Jones, *J. Amer. Chem. Soc.*, **63**, 3283 (1941).
(24) G. Wood and E. D. Woo, *Can. J. Chem.*, **46**, 3713 (1968).
(25) B. R. Vogt, *Tetrahedron Lett.*, 1579 (1968).
(26) C. D. Gutsche and T. D. Smith, *J. Amer. Chem. Soc.*, **82**, 4067 (1960); K. Biemann, "Mass Spectrometry—Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, p 246.
(27) P. v. R. Schleyer, E. Funke, and S. H. Liggero, *J. Amer. Chem. Soc.*, **91**, 3965 (1969).
(28) S. S. Guts and F. N. Stepanov, *Anilinokrasoch. Prom.*, **1**, 34 (1970); *Chem. Abstr.*, **77**, 34033 (1972).
(29) J. E. Nordlander, S. P. Jindal, P. v. R. Schleyer, R. C. Fort, Jr., J. J. Harper, and R. D. Nicholas, *J. Amer. Chem. Soc.*, **88**, 4475 (1966).
(30) H. Stetter and P. Goebel, *Chem. Ber.*, **96**, 550 (1963).
(31) H. Daniel and J. Paetsch, *Chem. Ber.*, **101**, 1445 (1968); W. K. Musker, *J. Org. Chem.*, **32**, 3189 (1967); G. Wittig and D. Krauss, *Justus Liebigs Ann. Chem.*, **679**, 34 (1964).
(32) For reports on migration of the adamantyl group, see B. L. Adams, J.-H. Liu, and P. Kovacic, *Tetrahedron Lett.*, 427 (1974); J. L. Fry, M. G. Adlington, R. C. Badger, and S. K. McCullough, *ibid.*, 429 (1974).
(33) S. H. Pine, B. A. Catto, and F. G. Yamagishi, *J. Org. Chem.*, **35**, 3663 (1970).
(34) U. Schöll kopf and U. Ludwig, *Chem. Ber.*, **101**, 2224 (1968).
(35) R. C. Fort, Ph.D. Thesis, Princeton University, 1964, cited in C. W. Woodworth, V. Buss, and P. v. R. Schleyer, *Chem. Commun.*, 569 (1968).
(36) Adduct **15** was found to be identical (ir, nmr, mass spectrum) with the corresponding product isolated from Cope elimination,[17] which gave satisfactory elemental analysis.
(37) The aromatic region was essentially identical with that for the DPIBF adducts of bicyclo[3.2.2]non-1-ene and bicyclo[3.2.1]oct-1-ene: J. A. Chong, Ph.D. Thesis, University of Michigan, 1971.

Rearrangement of *o*-Hydroxy Aldehydes and Ketones to *o*-Hydroxy Anilides by Monochloroamine[1]

Roy A. Crochet,[2a] F. Ryan Sullivan,[2b] and Peter Kovacic*

Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

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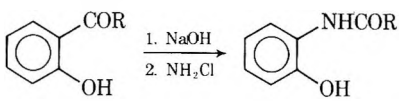
o-Hydroxy aldehydes and ketones are converted in good yield to *o*-hydroxy anilides by reaction with monochloroamine in base. The reaction was carried out with benzene nuclei containing alkyl, methoxyl, chlorine, and nitro substituents, as well as with the naphthalene nucleus. The overall transformation is similar to the Beckmann, Schmidt, Theilacker, and Pearson rearrangements. There appears to be mechanistic similarity to the Dakin oxidation.

The literature contains a number of rearrangement techniques for conversion of aromatic aldehydes and ketones to the corresponding anilides, including those of Beckmann,[3] Schmidt,[4] Theilacker,[5] and Pearson.[6] Each of these is characterized by certain limitations.

We have found a new method for the preparation of o-hydroxy anilides involving reaction of monochloroamine with variously substituted *o*-hydroxy aldehydes and ketones. This simple, one-step rearrangement, which takes place under mild conditions, comprises the preferred route for certain anilides. The mechanistic aspects were also investigated.

Results and Discussion

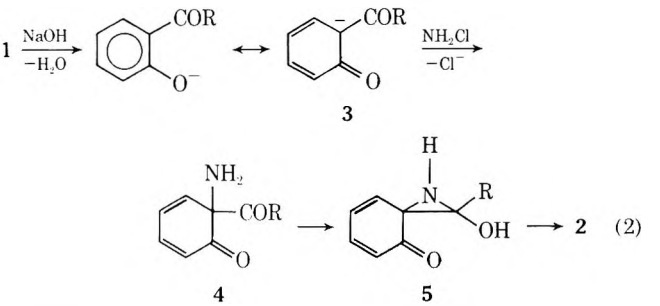
2-Acetamidophenol (**2a**) was obtained in essentially quantitative yield from addition of a caustic solution containing *o*-hydroxyacetophenone (**1a**) to aqueous monochloroamine at about 0°. The infrared spectrum of **2a** corresponded to that of authentic material. 2-Formamidophenol (**2b**), which displayed characteristic infrared absorption bands for the amide moiety, was obtained in similar manner in excellent yield from salicylaldehyde (**1b**). The melting points corresponded to the reported values. The structural assignments are also in agreement with the nmr spectra.



(1)

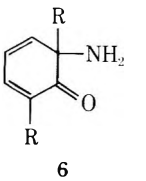
1a, R = CH_3 **2a**, R = CH_3
b, R = H **b**, R = H

The reaction pathway, eq 2, conceivably involves nucleophilic displacement of chloride ion from monochloroamine by the cyclohexadienone (phenoxide) anion (**3**) to produce amino ketone **4**. Intermediate **4** is then converted to aziridine **5**, which undergoes rearrangement to anilide **2**.



(2)

Formation of **4** is analogous to the postulate, involving **6**, advanced by Paquette for conversion of 2,6-disubstituted



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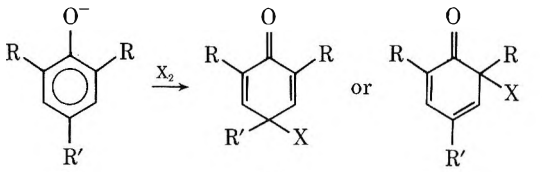
phenoxides into dihydroazepinones *via* ring expansion by exposure to monochloroamine.[7] Kornblum and coworkers noted that the extent of C-alkylation of phenoxides increased in hydroxylic solvent.[8]

An aziridine intermediate has also been invoked in the conversion of *N,N*-dichloroamines to α-amino ketones.[9] Monochloroamine has been used[10] for amination of malonic esters, perhaps *via* a route analogous to the transformation of **3** to **4**.

A factor weighing against involvement of dienone **4** is the difficulty of forming this type of species, according to the prior literature. Thus, it is reported[11a] that reaction of **7**

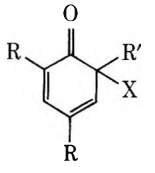
with halogen produces only **8** when R′ is electron donating (alkyl or methoxymethyl), eq 3. However, with an electron-



7 **8** **9**

R = alkyl (3)

withdrawing substituent (NO_2, CN, CHO, halogen) in the para position, the observed product is **9.** In addition, we were unable to find[11b] analogs of **8** (R′ = electron-withdrawing group) when electrophiles other than halogen were used, or compounds of type **10** (R′ = electron-withdrawing



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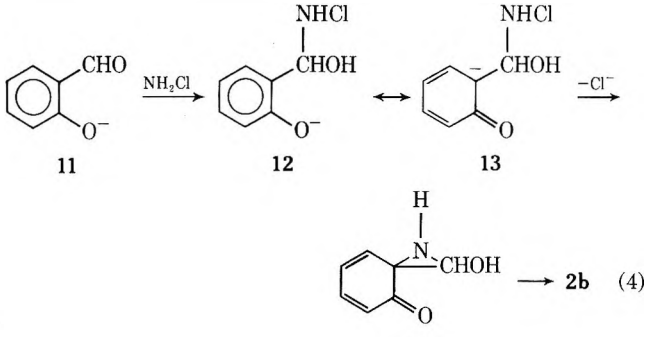
R = alkyl

group; X = electrophile). On the other hand, it is conceivable that reaction with NH_2Cl may be kinetically controlled, whereas certain other cases may reflect thermodynamic control.[11c]

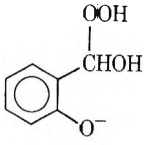
Benzaldehydes are known[12] to react with monochloroamine to produce *N*-chloroimines, presumably through the intermediacy of *N*-chlorocarbinolamines which might participate in our case, eq 4. The pathway depicted bears



11 **12** **13**

14 → **2b** (4)

resemblance to that suggested[13] for Dakin oxidation of *o*-hydroxy aldehydes and ketones to dihydroxybenzenes by means of alkaline peroxide, in which **15** may be involved.



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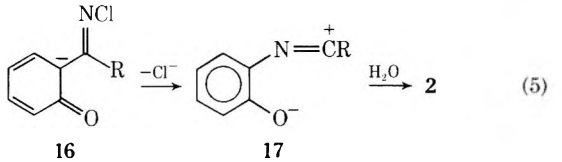
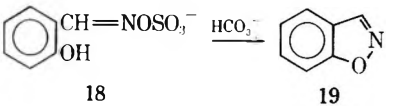
Our rearrangement, as well as that of Dakin, might well proceed in a concerted manner. A related example[14] entails transformation of *p*-$HOC_6H_4CH_2CH_2Br$ to spiro[2.5]octa-1,4-dien-3-one in the presence of base.

The *N*-chloroimine derivative (**16**) was given consideration as a possible intermediate, eq 5, somewhat similar to



16 **17** → **2** (5)

the Theilacker rearrangement.[5] However, there was no evidence for formation of this type of entity. In addition, acetophenone was recovered almost quantitatively when subjected to the standard procedure. It is significant that the *N*-chloroimine of acetophenone was stable when exposed to the usual conditions. In contrast, hydroxylammonium *O*-sulfonate combined with salicylaldehyde to give **18** which, on exposure to mild base, provided **19**,[15] eq 6.



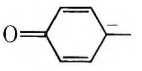
18 **19** (6)

Further evidence in opposition to **16** derives from the generation of *N*-methyl-2-acetamidophenol from methylmonochloroamine and *o*-hydroxyacetophenone in caustic solution. This appears to be the first example of an N,N-disubstituted amide arising from rearrangement of a carbonyl compound or its derivative.

Finally, one can visualize the existence of a nitrene,[16] acting as a precursor for **4**, from α-elimination involving monochloroamine. This approach bears resemblance to the synthesis of cyclohexadienones from substituted phenoxides and dichlorocarbene under Reimer–Tiemann conditions.[17] However, the elimination route appears unlikely since 67% of positive chlorine remained in a caustic solution of monochloroamine after 5 hr at 0°.

When the reaction between monochloroamine and *o*-hydroxyacetophenone was carried out at room temperature, rather than at 0°, 2,2′-dihydroxyacetophenone azine was isolated in addition to rearranged product. Apparently, under these conditions, hydrazine is formed[12] *in situ* from monochloroamine and excess ammonia, and subsequently condenses with the carbonyl-containing substrate.

Several experiments were conducted in order to determine the effect of the position of the hydroxyl group in the aromatic nucleus. In contrast to the situation with the corresponding ortho isomers, 4-formamidophenol and 4-acetamidophenol were obtained in only about 10% yield from *p*-hydroxylbenzaldehyde and *p*-hydroxyacetophenone, respectively. The poor results probably reflect the increased stability of the *p*-quinoid (**20**) *vs.* the corresponding *o*-qui-



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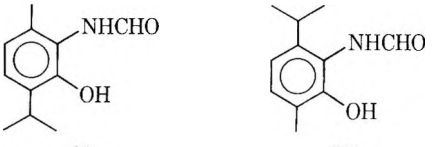
noid structure, or preference for an alternate pathway.[13] The importance of carbanion character associated with the nuclear carbon α to the carbonyl group (as in **3**) is indicated by the failure of *m*-hydroxyacetophenone and *o*-methoxyacetophenone to give rearranged products. Additional support for the crucial role of the *o*-hydroxyl group is provided by the absence of reaction with acetophenone.

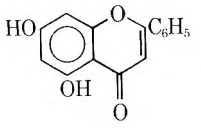
The scope of the reaction was explored in relation to the effect of various substituents in the salicylaldehyde nucleus. Methoxyl functioned well when situated adjacent to hydroxyl, providing 2-formamido-6-methoxyphenol in good yield. 3-Nitro- and 5-chlorosalicylaldehyde rearranged smoothly to the corresponding formamidophenols. Salicylaldehydes derived from naturally occurring thymol and carvacrol produced good yields of the corresponding formamides, **21** and **22**, respectively. Nuclear chlorination[12]



21 **22**

accompanied rearrangement with more highly activated aromatics, such as 4,6-dimethoxy-2-hydroxybenzaldehyde and 4,6-dimethyl-2-hydroxyacetophenone. With 2-hydroxy-1-naphthaldehyde, the corresponding amide, 1-formamido-2-naphthol, was provided. This may well be the preferred method for preparation of those products containing the methoxyl, chloro, and nitro groups. The anilides could then serve as precursors for the corresponding amines, as demonstrated in the hydrolysis of **2a** to *o*-aminophenol.

Variations were made in the nature of the substituents attached to the aroyl group in order to obtain further mechanistic and synthetic insight. In addition to **1a** and **1b**, *o*-benzoylphenol was examined, which afforded 2-benzamidophenol in 75% yield. More complex compounds containing the *o*-hydroxybenzoyl unit were explored. 1,8-Dihydroxyanthraquinone was not affected, possibly because of its low solubility in the medium. Chrysin (**23**) was recovered unchanged, whereas naringenin (**24**) yielded uncharacterized, high-melting material which was difficult to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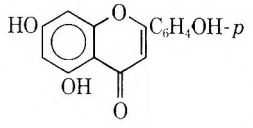
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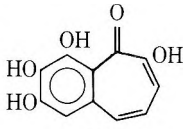
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purify. More drastic changes were made in the nature of the organic substrate. Tropolone was not altered and purpurogallin (**25**) gave unidentified, high-melting product. Several rationalizations come to mind concerning the failure of rearrangement in these cases: (1) in some instances a more highly strained cyclic amide would ensue, and (2) most of the substrates ontained the *p*-hydroxybenzoyl unit, which appears to affect rearrangement adversely (see above).

In a further study of reaction scope, related unsaturated groups were used in place of the carbonyl moiety. However, no rearrangement was observed with *o*-hydroxybenzonitrile, ethyl salicylate, or *N*-phenylsalicylamide. Concerning the observed specificity, contributing factors may be appropriate resonance stabilization of the carbanion (such as **3**) by the unsaturated substituent, and the fact that aldehydes and ketones are more susceptible to nucleophilic attack; see eq 4.

With few exceptions,[18] catalysts for Beckmann rearrangement of aromatic aldoximes produce little or no formanilides.[3] Thus, rearrangement of salicylaldoxime afforded only salicylamide in 47% yield with BF_3 catalyst.[3]

Mass spectral studies of several of the hydroxy anilide products (**2b, 22,** and 4-chloro-2-formamidophenol) revealed an intense M − 2 peak. This type of behavior has been previously reported for 1,4-dihydroxybenzenes.[19] In our case, iminoquinoid type moieties are presumably generated in the spectrometer. In addition, a strong M − 18 peak was observed, probably from formation of benzoxazoles.

Experimental Section

Ir spectra were obtained with KBr pellets. Elemental analyses were performed by Baron Consulting Co., Orange, Conn., and Dr. R. E. White. Anhydrous sodium sulfate was used for drying.

Preparation of Monochloroamine.[12] Cold (about 0°) aqueous solutions of 6% ammonia and 6% sodium hypochlorite were mixed in equal (w/w) percentage composition (NH_3:NaOCl = 2.8:1 M). The product molarity was determined by titration with 0.10 *N* sodium thiosulfate.

Preparation of Methylmonochloroamine.[12] A mixture of methylamine hydrochloride (0.06 mol) in 6% sodium hypochlorite (50 ml, 0.05 mol) was stirred for 30 min in an ice bath at *ca.* 0°. The product molarity was determined by titration with 0.10 *N* sodium thiosulfate.

General Procedure for Rearrangement. A solution of the *o*-hydroxy aldehyde or ketone (0.05 mol) in 100 ml of water containing sodium hydroxide (0.05 mol) was slowly added to a vigorously stirred solution of monochloroamine (0.05 mol) at about 0°. After the reaction mixture was agitated for 4 hr at about 0°, it was extracted with ether. The extract was dried, and solvent was removed under vacuum. In general, a negligible amount of residue was found. The cold, aqueous solution was acidified with cold 18% hydrochloric acid. At this stage either the precipitate was collected or the oil was taken up in ether. Removal of solvent from the dried extract afforded rearranged product which gave a light tan solid after crystallization, except for the nitro compound (yellow).

The indicated molar ratios were used in the individual cases, NH_2Cl:substrate: 0.02:0.0004, 1,8-dihydroxyanthraquinone; 0.02:0.01, **24;** 0.02:0.01, **25;** 0.02:0.01, **23;** 0.03:0.02, 2-hydroxy-3-methoxybenzaldehyde; 0.02:0.02, 2,4-dimethoxy-6-hydroxybenzaldehyde; 0.02:0.02, 2-hydroxy-3-nitrobenzaldehyde; 0.03:0.02, tropolone; 0.04:0.02, 1-formyl-2-naphthol; 0.01:0.01, *o*-benzoylphenol; 0.01:0.01, o-thymolaldehyde; 0.01:0.01, carvacrolaldehyde; 0.01:0.01, 2-hydroxy-4,6-dimethylacetophenone; 0.01:0.01, 5-chlorosalicylaldehyde.

Since 1,8-dihydroxyanthraquinone was found to be quite insoluble in the caustic medium, the quantity of base was doubled without apparent appreciable increase in solubility.

When the reaction was performed at 24° with **1a**, a precipitate of 2,2′-dihydroxyacetophenone azine was formed which was filtered and crystallized from ethanol: 4.6% yield; mp 197–198° (lit.[20a] mp 198°); ir 1608, 1300, 1249, 1158, 842, and 757 cm^{-1}; nmr ($CDCl_3$) δ 2.56 (s, 6 H), 6.80–7.70 (m, 8 H), and 9.50 (s, 2 H). Elemental analyses (C, H, N) were in accord with the formula $C_{16}H_{16}N_2O_2$. Rearranged product was obtained in 54% yield.

Characterization of Products. Compound **2a** was crystallized from a mixture of ether and petroleum ether (bp 35°): 99% yield; mp 203–205° (lit.[21,22] mp 203–204°); ir 3360, 3030, 1663, 1595, 1539, 1450, and 770 cm^{-1}; nmr (DMSO-d_6) δ 2.1 (s, 3 H), 6.9–7.8 (m, 4 H), 9.3 (s, 1 H), and 9.7 (s, 1 H). Elemental analyses (C, H, N) were in accord with the formula $C_8H_9NO_2$.

Compound **2b** was crystallized from a mixture of ether and petroleum ether: 87% yield; mp 127–128° (lit.[21] mp 129–129.5°); ir 3250, 2980, 1640, 1437, 1357, 870, 838, 756, and 744 cm^{-1}; nmr (DMSO-d_6) δ 6.60–7.15 (m, 4 H), 8.30 (s, 1 H), 9.50 (broad s, 1 H), and 9.83 (s, 1 H).

2-Formamido-6-methoxyphenol was crystallized from a mixture of ether and petroleum ether: 75% yield; mp 123–124°; ir 3260, 3060, 1665, 1470, 1265, 1222, 1068, 903, and 704 cm^{-1}; nmr (DMSO-d_6) δ 3.87 (s, 3 H), 6.60–6.90 (d, 2 H), 7.6–7.9 (m, 1 H), and 9.23 (s, 1 H).

Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.56; H, 5.63; N, 8.34.

1-Formamido-2-naphthol was crystallized from a mixture of benzene and cyclohexane: about 24% yield; mp 205–206° (lit.[20b] mp 204°); ir 3205, 1665, 1508, 1318, 980, 772, and 760 cm^{-1}; nmr (DMSO-d_6) δ 6.99–8.00 (m, 6 H), 8.33 (s, 1 H), and 9.13–10.10 (q, 2 H).

2-Formamido-6-nitrophenol was crystallized from a mixture of benzene and cyclohexane: 99% yield; mp 168–169°; ir 3210, 1670, 1605, 1527, 1258, 924, and 748 cm^{-1}; nmr (DMSO-d_6) δ 6.63–7.01 (t, 1 H), 7.55–7.80 (d, 1 H), 8.42 (broad s, 2 H), 9.97 (br, 1 H), 10.66 (br, 1 H).

Anal. Calcd for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.01; H, 3.55; N, 15.36.

2-Benzamidophenol was crystallized from a mixture of ether and petroleum ether: 75% yield; mp 166.5–167.5° (lit.[23] mp 167°); ir 3320, 2970, 1642, 1532, 1445, 750, 705, and 688 cm^{-1}; nmr (DMSO-d_6) δ 6.70–8.20 (m, 9 H), 9.56 (s, 1 H), and 9.76 (s, 1 H).

N-Methyl-2-acetamidophenol was crystallized from a mixture of ether and petroleum ether: 19% yield; mp 152–153°; ir 3210, 1642, 1490, 836, and 765 cm^{-1}; nmr ($CDCl_3$) δ 1.90 (s, 3 H), 3.24 (s, 3 H), 6.70–7.30 (m, 4 H), and 8.95–9.40 (broad s, 1 H).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.04; H, 6.67; N, 8.42.

3-Isopropyl-6-methyl-2-formamidophenol (**22**) was crystallized from a mixture of benzene and petroleum ether: 75% yield; mp 144–146°; ir 3250, 1630, 1600, 807, and 741 cm^{-1}; nmr (acetone-d_6) δ 1.12 (d, 6 H), 2.10 (s, 3 H), 2.95 (s, 1 H), 3.00 (m, 1 H), 6.84 (q, 2 H), 7.88 (s, 1 H), and 8.32 (s, 1 H).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.65; H, 7.98; N, 7.22.

6-Isopropyl-3-methyl-2-formamidophenol (**21**) was crystallized from a mixture of benzene and petroleum ether: 76% yield; mp

135–136°; ir 3180, 1670, 1605, 808, and 715 cm^{-1}; nmr (acetone-d_6) δ 1.20 (d, 6 H), 2.24 (s, 3 H), 3.03 (s, 1 H), 3.38 (m, 1 H), 6.87 (q, 2 H), 8.20 (s, 1 H), and 8.32 (s, 1 H).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.51; H, 7.92; N, 7.24.

4-Chloro-2-formamidophenol was crystallized from a mixture of benzene and petroleum ether: 74% yield; mp 156–157.5°; ir 3300, 3025, 1660, 1475, 1205, 1110, and 803 cm^{-1}; nmr (DMSO-d_6) δ 6.73 (s, 2 H), 8.03 (s, 1 H), 8.20 (s, 1 H), 9.45 (s, 1 H), and 9.83 (broad, 1 H).

Anal. Calcd for $C_7H_6NO_2Cl$: C, 49.00; H, 3.53; N, 8.16; Cl, 20.66. Found: C, 48.87; H, 3.70; N, 8.20; Cl, 20.77.

4- (or 6-) chloro-3,5-dimethoxy-2-formamidophenol, from 4,6-dimethoxysalicylaldehyde, was crystallized repeatedly from a mixture of benzene and cyclohexane: 17% yield; mp 145–146°; ir 3300, 3060, 1610, 1465, 1120, and 794 cm^{-1}; nmr (DMSO-d_6) δ 3.97 (s, 6 H), 6.50 (s, 1 H), 8.16 (s, 1 H), 8.50 (br, 1 H), and 9.50 (s, 1 H).

Anal. Calcd for $C_9H_{10}NO_4Cl$: C, 46.66; H, 4.35; N, 6.05; Cl, 21.15. Found: C, 46.86; H, 4.39; N, 6.17; Cl, 20.77.

Elemental analysis and the nmr spectrum of the reaction product after only two crystallizations indicated the presence of a mixture composed of chlorinated product (35%) and 3,5-dimethoxy-2-formamidophenol (65%). An attempt to prepare the unchlorinated material by use of excess aldehyde (2:1 molar ratio of aldehyde: NH_2Cl) gave a mixture of the two products (tlc). The chlorinated substance was isolated by repeated crystallization, but the other component was not cleanly separated.

4- (or 6-) chloro-3,5-dimethyl-2-acetamidophenol, obtained from 4,6-dimethyl-2-hydroxyacetophenone, was crystallized repeatedly from a mixture of benzene and petroleum ether: 22% yield; mp 179–181.5°; ir 3300, 3110, 1610, 1485, 1010, and 850 cm^{-1}; nmr (DMSO-d_6) δ 2.00 (s, 3 H), 2.10 (s, 3 H), 2.23 (s, 3 H), 6.67 (s, 1 H), 8.97 (s, 1 H), and 9.10 (s, 1 H).

Anal. Calcd for $C_{10}H_{12}NO_2Cl$: C, 56.21; H, 5.62; N, 6.55; Cl, 16.59. Found: C, 56.07; H, 5.71; N, 6.24; Cl, 16.33.

2-Hydroxy-4,6-dimethylacetophenone. A prior procedure[24] was used. Recrystallization from benzene gave a light yellow solid (10%), mp 57–57.5° (lit.[24] mp 57–58.5°).

o-Carvacrolaldehyde. A previous method[25] was used. Distillation provided a yellow liquid (12%): bp 81–84° (4 mm); nmr δ 12.20 (s, 1 H), 11.90 (s, 1 H), 7.09 (d, 1 H), 6.52 (d, 1 H), 3.44 (m, 1 H), 2.10 (s, 3 H), and 1.12 (d, 6 H).

o-Thymolaldehyde. A literature procedure[25] was used. Distillation gave a yellow liquid (10%): bp 79–80° (4 mm); nmr δ 12.20 (s, 1 H), 11.80 (s, 1 H), 6.43 (d, 1 H), 3.20 (m, 1 H), 2.39 (s, 3 H), 1.10 (d, 6 H).

5-Chlorosalicylaldehyde. Use of a published method[25] gave light yellow crystals (9% yield), mp 96–98° (lit.[25] mp 99°), from steam distillation.

N-Chloroacetophenonimine.[12] *N,N*-Dichloro-α-methylbenzylamine[26] (1.9 g, 0.01 mol) was added dropwise to a solution of potassium acetate (2.5 g, 0.025 mol) in absolute ethanol (13 ml) at reflux. The mixture was then refluxed for 30 min, cooled, and poured into water. After extraction with ether, the organic solution was dried and then freed of solvent, yielding 1.2 g (80%) of a yellow liquid. Titration with sodium thiosulfate indicated a purity of 83%; ir 3025, 1705, 1620, 1585, 758, and 692 cm^{-1}; nmr (CCl_4) δ 2.47 (s, 3 H) and 7.20–7.91 (m, 5 H).

Hydrolysis of 2-Acetamidophenol. 2-Acetamidophenol (5 g) was heated in concentrated HCl (50 ml) at reflux for 2 hr. After the mixture was cooled and neutralized with $NaHCO_3$, the crystals were collected, 1.1 g, mp 170–173° (lit.[20c] mp 174°). The ir spectrum was identical with that of an authentic sample of 2-aminophenol. The residual solution was evaporated to dryness and extracted with methanol. Removal of solvent from the dried solution provided 2 g of crude product.

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Registry No.—**1a,** 118-93-4; **1b,** 90-02-8; **2a,** 614-80-2; **2b,** 2843-27-8; **21,** 52260-17-0; **22,** 52260-18-1; **23,** 480-40-0; **24,** 480-41-1; monochloroamine, 10599-90-3; 1,8-dihydroxyanthraquinone, 117-10-2; 2-hydroxy-3-methoxybenzaldehyde, 148-53-8; 2,4-dimethoxy-6-hydroxybenzaldehyde, 708-76-9; 2-hydroxy-3-nitrobenzaldehyde, 5274-70-4; 1-formyl-2-naphthol, 708-06-5; o-benzoylphenol, 117-99-7; o-thymolaldehyde, 1666-00-8; o-carvacrolaldehyde, 1665-99-2; 2-hydroxy-4,6-dimethylacetophenone, 16108-50-2; 5-chlorosalicylaldehyde, 635-93-8; 2,2′-dihydroxyacetophenone, 17375-96-1; 2-formamido-6-methoxyphenol, 51029-17-5; 1-formamido-2-naphthol, 52260-19-2; 2-formamido-6-nitrophenol, 52260-20-5; 2-benzamidophenol, 3743-70-2; *N*-methyl-2-acetamidophenol, 573-27-3; 4-chloro-2-formamidophenol, 31354-50-4; 4-(or 6-) chloro-3,5-dimethoxy-2-formamidophenol, 52341-47-6; 3,5-dimethoxy-2-formamidophenol, 52260-21-6; 4- (or 6-) chloro-3,5-dimethyl-2-acetamidophenol, 52341-48-7; *N*-chloroacetophenonimine, 52260-22-7; *N,N*-dichloro-α-methylbenzylamine, 34863-18-8.

References and Notes

(1) Paper XXII, Chemistry of *N*-Haloamines. Preliminary communication: R. A. Crochet and P. Kovacic, *J. Chem. Soc., Chem. Commun.*, 716 (1973).
(2) Postdoctoral Fellow, (a) 1972–1973; (b) 1973–1974.
(3) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11,** 1 (1960).
(4) P. A. S. Smith, "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 518.
(5) W. Theilacker and H. Mohl, *Justus Liebigs Ann. Chem.*, **563,** 99 (1949).
(6) C. A. Buehler and D. E. Pearson, "Survey of Organic Syntheses," Wiley-Interscience, New York, N. Y., 1970, p 494.
(7) L. A. Paquette, *J. Amer. Chem. Soc.*, **85,** 3288 (1963).
(8) N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Amer. Chem. Soc.*, **85,** 1141 (1963).
(9) H. E. Baumgarten and F. A. Bower, *J. Amer. Chem. Soc.*, **76,** 4561 (1954).
(10) M. Horiji, J. Oda, Y. Inouye, M. Ohno, and K. Matsumoto, Japanese Patent 7,100,165 (1971); *Chem. Abstr.*, **74,** 124863 (1971).
(11) (a) A. J. Waring, *Advan. Alicyclic Chem.*, **1,** 174 (1966); (b) *ibid.*, **1,** 129 (1966); (c) we thank a reviewer for this suggestion.
(12) P. Kovacic, M. K. Lowery, and K. W. Field, *Chem. Rev.*, **70,** 639 (1970).
(13) M. B. Hocking, *Can. J. Chem.*, **51,** 2384 (1973); it is interesting to compare Scheme 4 in this reference with our results involving *p*-hydroxybenzaldehyde.
(14) R. Baird and S. Winstein, *J. Amer. Chem. Soc.*, **85,** 567 (1963).
(15) D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21,** 3019 (1965).
(16) C. A. Wilkie and D. R. Dimmel, *J. Amer. Chem. Soc.*, **94,** 8600 (1972).
(17) H. Wynberg, *Chem. Rev.*, **60,** 169 (1960).
(18) M. G. Deshmush and K. C. Jain, *Indian J. Chem.*, **6,** 337 (1968); *Chem. Abstr.*, **69,** 85930 (1968).
(19) R. T. Aplin and W. T. Pike, *Chem. Ind. (London)*, 2009 (1966).
(20) "Dictionary of Organic Compounds," J. R. A. Pollock and R. Stevens, Ed., Oxford University Press, London, 1965: (a) Vol. 3, p 1639; (b) Vol. 1, p 170; (c) Vol. 1, p 193.
(21) E. Bamberger, *Ber.*, **36,** 2042 (1903).
(22) A. Ladenburg, *Ber.*, **9,** 1524 (1876).
(23) G. Ciamician and P. Silber, *Ber.*, **38,** 1176 (1905).
(24) L. I. Smith and J. W. Opie, *J. Org. Chem.*, **6,** 427 (1941).
(25) J. C. Duff, *J. Chem. Soc.*, 547 (1941).
(26) T. A. Kling, R. E. White, and P. Kovacic, *J. Amer. Chem. Soc.*, **94,** 7416 (1972).

Chemistry of α-Halo Aldehydes. V.[1] Reaction of α-Halo Aldehydes with α-Acetylcyclopentanones in the Presence of Base[2]

Akira Takeda,* Sadao Tsuboi, Fumitaka Sakai, and Mamoru Tanabe

Department of Synthetics Chemistry, School of Engineering, Okayama University, Tsushima, Okayama, Japan 700

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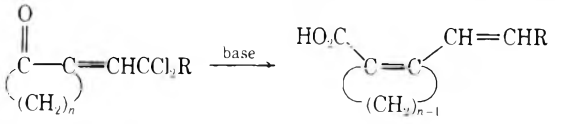
Reaction of chloral with 2-acetylcyclopentanone (**3a**) in the presence of potassium carbonate in tetrahydrofuran spontaneously yielded 2-(2′-chlorovinyl)cyclobutenecarboxylic acid (**6a**). The pathway, which involves the transient existence of α-(2,2,2-trichloroethylidene)cyclopentanone (**4a**) followed by the Favorskii-type rearrangement, has been postulated for the formation of **6a**. The reaction of chloral with 1-morpholino-1-cyclopentene (**8a**) gave 2-(2′,2′,2′-trichloro-1′-hydroxyethyl)cyclopentanone (**9a**). The dehydration of **9a** with H_2SO_4 led to the formation of 2-(2′,2′-dichlorovinyl)-2-cyclopentenone (**10a**). The treatment of **9a** with alkali failed to give **6a**. The analogous reaction of dichloroacetaldehyde with α-acetylcyclopentanone gave 5-acetyl-7,7-dichloro-5-heptenoic acid (**14a**). The reaction of acetylcyclohexanone with chloral solely resulted in the recovery of the starting material.

We have been studying the chemical properties of α-(2-haloalkylidene) ketones. In the previous paper,[3] we reported that α-(2,2,2-trichloroethylidene)acetone as well as the related compounds (**1**) underwent Favorskii-type rearrangement as the vinylogs of α-chloroacetone to give 2,4-pentadienoic acid derivatives (**2**). As an extension of previ-

$$\underset{\mathbf{1}}{RCCl_2CH{=}CHCOCH_3} \xrightarrow{HO^-} \underset{\mathbf{2}}{RCH{=}CHCH{=}CHCO_2H}$$

ous works,[1,3] we were interested in investigating the Favorskii-type rearrangement of five- and six-membered ring systems such as α-(2-chloroalkylidene)cyclopentanone (**4**) and α-(2-chloroalkylidene)cyclohexanone (**5**) in order to find out a new route leading to ring-contracted cycloalkenecarboxylic acids (**6**). To obtain halogenated alkyli-



4, $n = 3$
5, $n = 4$

6

denecycloalkanones **4** and **5**, the procedure, which we[3,4] devised for the preparation of halogenated α-alkylideneacetone **1** has been adapted. It involves the reaction of α-halo aldehyde with α-acetylcycloalkanone (**3**) in the presence of potassium carbonate in tetrahydrofuran (THF). The attempted reaction of α-acetylcyclohexanone, however, failed to afford the desired product (**5**). Although we were unsuccessful in isolating the intermediate α-alkylidenecyclopentanone **4** in the reaction of α-acetylcyclopentanone with α-chloro aldehydes, there are evidences for the fact that a crossed aldol condensation has preceded, since the final products it gave were apparently those derived by ring cleavage or by ring contraction of the appropriate condensation products. This paper will describe and discuss the results of these reactions. Structures of the products were determined principally based on both spectral data and elemental analysis. Oxidative degradations of the ethylenic products were also carried out in order to substantiate the structural assignments.

Results and Discussion

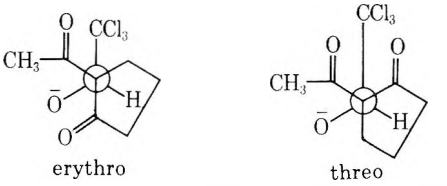
It has already been found that the base-catalyzed condensation of chloral with acetylacetone affords α-(2,2,2-trichloroethylidene)acetone in good yield.[4] In contrast, the reaction of α-acetylcyclopentanone (**3a**) with chloral gave, not the expected α-(2,2,2-trichloroethylidene)cyclopentanone (**4a**), but 2-(2′-chlorovinyl)cyclobutenecarboxylic acid (**6a**) in 32% yield.[5] An absorption band at 1565 cm^{-1} in ir spectrum of **6a**[6] and singlet (4 H) at 2.50 ppm in its nmr spectrum strongly indicated the presence of cyclobutene ring.[7] The mass spectrum of **6a** showed clear molecular ions at *m/e* 158 with the characteristic chlorine isotope distribution. The fact that Favorskii-type products have never been isolated from the basic treatment of α-chlorocyclopentanones[8] prompted us to examine its generality for other α-acylcyclopentanone and chloro aldehydes. Thus, 2-acetyl-4-methylcyclopentanone (**3b**) with chloral afforded 2-(2′-chlorovinyl)-4-methylcyclobutenecarboxylic acid (**6b**) in a 21% yield along with a small amount (yield 4%) of 2-(2′,2′-dichlorovinyl)-4-methyl-2-cyclopentenone (**10b**). The treatment of **6a** with diazomethane yielded its methyl ester (**7**), which gave the correct analysis.[9] Undoubtedly, the cyclopentenone **10b** is considered to have been derived from its precursor **4b**, which has for the most part undergone Favorskii-type rearrangement to give **6b**. The structure of **6** has been further confirmed by its oxidative degradation to succinic acid. For instance, the treatment of **6b** with aqueous potassium permanganate gave methylsuccinic acid[10] in a 43% yield. Reflecting the chemical properties of straight-chained analogs like **1**,[3] the pathway, which involves the transient existence of α-ethylidenecyclopentanone **4** followed by the Favorskii-type rearrangement, can be reasonably postulated for the formation of **6** as is shown in Scheme I. Compound **4**, if generated, however, seems to be labile at the condition concerned, since several reactions attempted for preparing **4** all turned out to be a failure.

The reaction of chloral with 1-morpholino-1-cyclopentene (**8a**) and its 4-methyl derivative (**8b**) gave 2-(2′,2′,2′-trichloro-1′-hydroxyethyl)cyclopentanone (**9a**) and its 4-methyl derivative (**9b**) in 61 and 53% yields, respectively. The dehydration of **9a** and **9b** with H_2SO_4 caused a concurrent dehydrochlorination to yield 2-(2′,2′-dichlorovinyl)-2-cyclopentenone (**10a**) and its 4-methyl derivative (**10b**) (Scheme II). The treatment of **9a** with $SOCl_2$ afforded 2-(1′,2′,2′,2′-tetrachloroethyl)cyclopentanone (**11**) in a 13% yield. The dehydrochlorination of compound **11** also failed to give **4a**. While α-hydroxy ketones such as 5,5,5-trichloro-4-hydroxy-2-pentanone (chloralacetone) and 5,5-dichloro-4-hydroxy-2-pentanone yielded the appropriate 2,4-pentadienoic acids behaving as precursors of α-(2,2,2-trichloroethylidene)acetone and α-(2,2-dichloroethylidene)acetone,[3] cyclic hydroxy ketones **9a** and **9b** only gave an intractable, resinous material when they were subjected to the treatment with alkali.

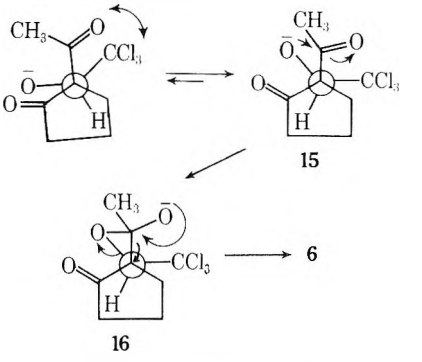
The behavior of dichloroacetaldehyde toward **3a** was in a striking contrast to that of chloral. The base-catalyzed con-

densation of **3a** with dichloroacetaldehyde in THF gave 5-acetyl-7,7-dichloro-5-heptenoic acid (**14a**, yield 36%) in place of Favorskii-type product. When the reaction was conducted in water, the yield was increased to 59%. The acid **14a** was converted to methyl ester **14b** with diazomethane in order to facilitate the purification. The ir band at 1740 cm^{-1} supported the presence of unconjugated ester carbonyl. The nmr spectrum of **14b** in carbon tetrachloride showed the signal due to one olefinic proton and one C-7 methine proton as a singlet (2 H) at δ 6.70 ppm, and that due to ester methyl protons as a singlet at 3.66 ppm. The signal due to acetyl methyl protons appeared at 2.37 ppm as a singlet. The mass spectrum of **14b** showed a strong peak at m/e 217 ($M^+ - Cl$). The permanganate oxidation of **14a** yielded glutaric acid in a 54% yield together with a small amount of succinic acid.[11] The reaction sequence for the formation of the acid **14a** is shown in Scheme III, in which the condensation product **12** undergoes a retro acetoalkanoate reaction.[12]

The oxy anions **12** and **15**, which are produced primarily in these reactions, are considered to be of erythro forms,

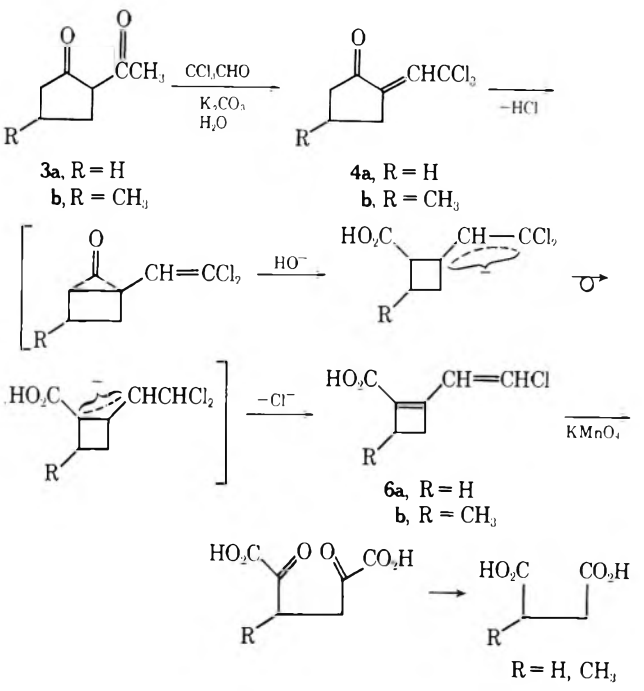


i.e., less hindered, hence more stable ones. Whether electronic or steric, the polychloromethyl group of these intermediates obviously has an effect in determining the product. While the oxy anion of **12** is readily arranged eclipsed to and can attack the ring carbonyl of cyclopentanone to form a possible intermediate **13**, the bulkiness of trichloromethyl group as compared to dichloromethyl group does not allow the oxy anion of **15** to take the same arrangement as **12** at the transition state. It can be arranged eclipsed to acetyl carbonyl more readily to form the intermediate **16**, which is then converted to **6**.

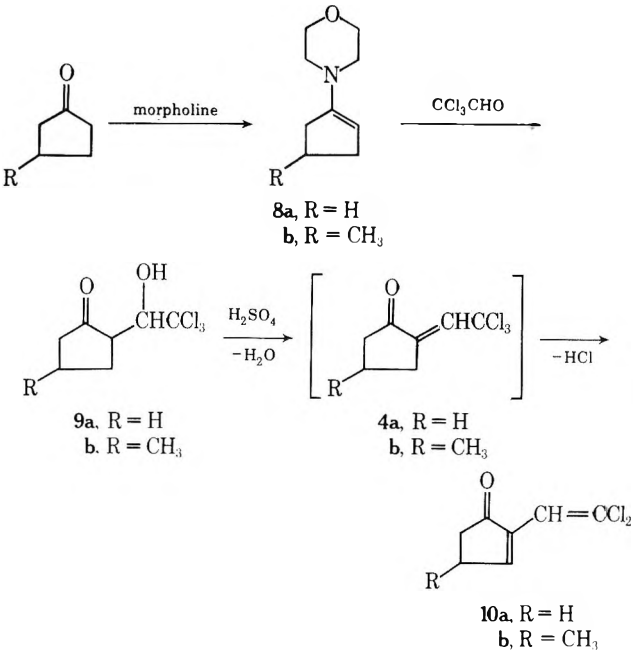


It was rather surprising that the reaction of α-acetylcyclohexanone with chloral resulted in the recovery of the starting material. It may be attributable in part to the hindrance caused by axial hydrogens of acetylcyclohexanone, which disturbs its approach to chloral. As compared to cy-

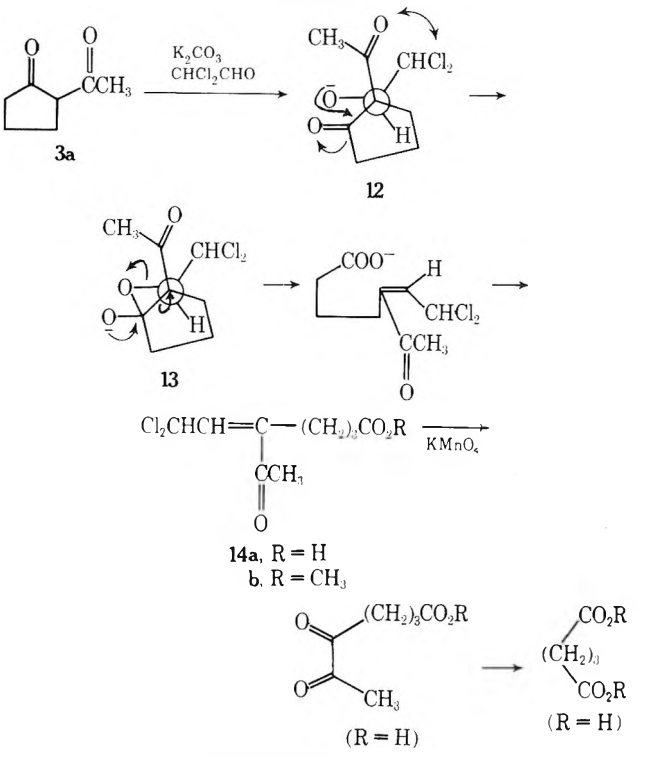
Scheme I



Scheme II



Scheme III



clohexanone ring, the carbanion of acetylcyclopentanone appears less masked by ring protons.

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano of our laboratory. The analytical determinations by glpc were performed on a Hitachi Model K-53 gas chromatograph (3 mm o.d. × 1 m, 10% Apiezon grease L on Chromosorb W column); carrier gas, N_2 (0.5 kg/cm^2, 40 ml/min); detector, FID. The preparative glpc was performed on a Yanagimoto Model GCG-550T gas chromatograph (3 mm o.d. × 2.25 m, 10% Apiezon grease L on Chromosorb W column; detector, TCD). Analytical thin layer chromatography (tlc) was done on silica gel GF_{254} (E. Merck AG, Darmstadt) with layers of 0.2-mm thickness. Preparative tlc was done on silica gel PF_{254} (E. Merck AG, Darmstadt) with plates of 20 × 20 cm^2 and 1.0-mm thickness. Mass spectra were run on a Hitachi Model RMS-4 mass spectrometer and nmr spectra were obtained on a Hitachi Model R-24 spectrometer (60 MHz). Commercial grade THF, which was purified by distillation after being treated with Na_2SO_4 overnight, was used.

α-Acetylcyclopentanone (**3a**) was prepared by the method described in the literature,[13] using 1-morpholino-1-cyclopentene (**8a**) and acetyl chloride, bp 80–85° (12 mm) [lit.[14] bp 75° (8 mm)]. α-Acetyl-4-methylcyclopentanone (**3b**) was prepared in a way similar to **3a**: yield 64%; bp 61.5° (3 mm); ir (neat) 1738 (C=O), 1705 (C=O), 1650, and 1610 cm^{-1}; nmr ($CDCl_3$) δ 1.11 (d, 3, CH_3), 1.96 (s, 3, $COCH_3$), 2.00–3.10 (m, 5, C_3, C_4, and C_5H), and 3.20–3.80 ppm (m, 1, C_2H).

2-(2′-Chlorovinyl)cyclobutenecarboxylic Acid (6a). To a mixed solution of 1.3 g (0.01 mol) of **3a** and 1.5 g (0.01 mol) of chloral in 10 ml of dry THF was added 1.8 g (0.013 mol) of anhydrous potassium carbonate in several portions. After being stirred at room temperature for 1 hr and then at 32–34° for 5 hr, the mixture was poured into 30 ml of water and acidified with 10% hydrochloric acid. The organic layer was extracted with ether and the ethereal extract was dried over $MgSO_4$. After removal of the solvent, the residue was distilled to give 0.5 g of **6a**: yield 32%; bp 116–120° (5 mm); mp 118–119° (benzene); ir (KBr) 2300–3400 (COOH), 1665 (C=O), 1630 (C=C), and 1565 cm^{-1} (cyclobutene C=C); nmr ($CDCl_3$) δ 2.50 (s, 4, cyclobutene ring protons), AB quartet centered at 6.62 and 7.03 (2, J = 14 Hz, –CH=CHCl), 6.50–7.10 ppm (broad s, 1, COOH); mass spectrum (70 eV) *m/e* (rel intensity) 158 (18, M$^+$, 1 Cl), 123 (100, M$^+$ − Cl).

Anal. Calcd for $C_7H_7ClO_2$: C, 53.02; H, 4.45. Found: C, 52.84; H, 4.26.

Methyl 2-(2′-Chlorovinyl)cyclobutenecarboxylate (7). To a solution of 0.35 g (0.0022 mol) of **6a** in 3 ml of dry ether was added an ethereal solution of diazomethane (*ca.* 0.7 mol/l.) in several portions at −30° until evolution of nitrogen ceased. After the mixture was allowed to stand for 30 min, distillable material (unreacted diazomethane and the solvent) was removed *in vacuo*. Tlc analysis[15] of the residue (0.37 g) showed two spots at R_f values of 0.42 and 0.26, in a ratio of 10:7. The compound with the R_f value of 0.42 was collected by preparative tlc and identified as **7**: yield 57%; ir (neat) 1690 (C=O), 1610 (C=C), and 1565 cm^{-1} (cyclobutene C=C); nmr ($CDCl_3$) δ 2.47 (broad s, 4, cyclobutene ring protons), 3.97 (s, 3, $COOCH_3$), AB quartet centered at 6.54 and 6.96 ppm (2, –CH=CHCl); mass spectrum (70 eV) *m/e* (rel intensity) 172 (36, M$^+$), 137 (85, M$^+$ − Cl), 95 (100), 87 (42), 65 (52), 52 (34), 43 (66).

Anal. Calcd for $C_8H_9ClO_2$: C, 55.67; H, 5.25. Found: C, 55.55; H, 5.25.

The compound with the R_f value of 0.26 was similarly collected and analyzed: mp 83.5–84.5°; ir (KBr) 1780, 1705, 1632, and 1574 cm^{-1}; nmr ($CDCl_3$) δ 2.28 (s), 2.40–2.88 (m), and 6.79 ppm (s); mass spectrum (70 eV) *m/e* (rel intensity) 200 (2.4, 1 Cl), 158 (19, 1 Cl), 123 (100), 87 (6), 51 (13), 43 (17).

Anal. Found: C, 53.92; H, 3.97.[16]

2-(2′-Chlorovinyl)-4-methylcyclobutenecarboxylic Acid (6b). To a mixed solution of 4.0 g (0.028 mol) of **3b** and 5.3 g (0.036 mol) of chloral in 30 ml of dry THF was added 8.3 g (0.06 mol) of anhydrous potassium carbonate in several portions. After being stirred at room temperature for 1 hr and then at 30–35° for 5 hr, the mixture was poured into 100 ml of water. The organic layer (neutral portion) was extracted with ether and then the ethereal extract was washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was distilled to give 1.2 g of oil, bp 81–115° (0.1 mm). Tlc analysis[17] of this oil showed two spots at R_f values of 0.34 and 0.60, in a ratio of 4:1. The compound with the R_f value of 0.34 collected by preparative tlc was identified as **6b**: yield[18] 21%; mp 59.5–60.5°; ir (KBr) 2000–3450 (COOH), 1675 (C=O), 1645 (C=C), and 1575 cm^{-1} (cyclobutene C=C); nmr ($CDCl_3$) δ 1.19 (d, 3, J = 7.5 Hz, CH_3), 1.98–3.02 (m, 3, cyclobutene ring protons), AB quartet centered at 6.57 and 7.00 ppm (2, J = 14 Hz, –CH=CHCl), 6.50–7.40 (broad s, 1, COOH); mass spectrum (70 eV) *m/e* (rel intensity) 172 (82, M$^+$), 138 (63), 137 (100, M$^+$ − Cl), 109 (64), 102 (52), 81 (54), 79 (54), 71 (50), 53 (59).

Anal. Calcd for $C_8H_9ClO_2$: C, 55.67; H, 5.25. Found: C, 55.68; H, 5.32.

The compound with the R_f value of 0.60 was similarly collected and identified as **10b**: yield 4%; ir (neat) 1710 (C=O), 1620 (C=C), and 1600 cm^{-1} (C=C); nmr (CCl_4) δ 1.28 (d, 3, J = 7.5 Hz, CH_3), 1.87 (q, 1, J = 18 and 2.5 Hz, C_5 H), 3.0 (m, 1, C_4 H), 6.55 (s, 1, –CH=CCl_2), and 7.93 ppm (d, 1, J = 3 Hz, C_3 H); mass spectrum (70 eV) *m/e* (rel intensity) 190 (20, M$^+$, 2 Cl), 175 (10, M$^+$ − CH_3), 155 (100, M$^+$ − Cl), 147 (14), 127 (33), 91 (26), 77 (20).

Anal. Calcd for $C_8H_8Cl_2O$: C, 50.29; H, 4.22. Found: C, 50.07; H, 4.23.

Oxidation of 6b with Potassium Permanganate. To a solution of 0.494 g (0.0031 mol) of potassium permanganate in 6.6 ml of water was added in one portion a solution of 0.06 g (0.35 mmol) of **6b** in aqueous potassium hydroxide (0.057 g of KOH, and 1.4 ml of water) at 35°. After being stirred for 30 min at 75°, the mixture was acidified with dilute sulfuric acid (0.35 ml of concentrated sulfuric acid and 1.07 ml of water) and then heated on a steam bath for 15 min to coagulate the manganese dioxide, which was filtered while hot. The filtrate was evaporated to a volume of about 2 ml. The ethereal extract of the organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent the residue gave 0.040 g of a solid, which was recrystallized from *n*-hexane, giving 0.020 g (43%) of methylsuccinic acid, mp 107–109° (*n*-hexane) (lit.[10] mp 110–111°). Ir and nmr spectra were identical with those of an authentic sample.[10]

Oxidation of 6a with potassium permanganate was carried out in the same way as that of **6b**, and the white crystals obtained was identified as succinic acid by comparison of ir and nmr spectra with those of an authentic sample.

2-(2′,2′,2′-Trichloro-1′-hydroxyethyl)cyclopentanone (9a). To a solution of 10.7 g (0.07 mol) of **8a** in 35 ml of dry chloroform was added a solution of 10.6 g (0.072 mol) of chloral in 15 ml of dry chloroform at room temperature over a 1-hr interval. The mixture was stirred for 1 hr and then 35 ml of 20% HCl was added. After the mixture was refluxed for 5 hr, it was cooled and the organic layer was separated. The aqueous layer was adjusted to a pH of about 6 with a 25% aqueous NaOH and then the organic layer was extracted with chloroform. The combined extract was washed with saturated sodium chloride and dried over $MgSO_4$. Removal of the solvent left a crude crystalline product which gave 9.8 g (61%) of **9a**: mp 126–127° (benzene); ir (Nujol) 3400 (OH), 1720 (C=O), 800, and 820 cm^{-1}; nmr ($CDCl_3$) δ 1.90–2.50 (m, 6, C_3, C_4, C_5H), 2.75 (m, 1, C_2 H), 3.47 (s, 1, OH), and 4.70 ppm (broad d, 1, J = 1.6 Hz, >CHOH).

Anal. Calcd for $C_7H_9Cl_3O_2$: C, 36.32; H, 3.92. Found: C, 36.11; H, 3.58.

2-(2′,2′,2′-Trichloro-1′-hydroxyethyl)-4-methylcyclopentanone (9b) was prepared from **8b** (15.8 g, 0.095 mol) and chloral (14.7 g, 0.1 mol) in the same way as in the preparation of **9a**. The crude product was distilled to give 12.1 g (53%) of **9b**: bp 120–122° (0.2 mm); ir (neat) 3480 (OH), 1742 (C=O), 1160, 1120, 820, and 740 cm^{-1}; nmr ($CDCl_3$) δ 1.08 and 1.26 (2 d,[19] 3, J = 6.5 Hz, CH_3), 1.50–2.70 (m, 5, C_3, C_4, C_5 H), 3.00 (m, 1, C_2 H), 3.47 (broad s, 1, OH), 4.71 ppm [broad s, 1, >CH(OH)]; mass spectrum (70 eV) *m/e* (rel intensity) 244 (0.4, M$^+$, 3 Cl), 209 (21, M$^+$ − 2 Cl), 127 (83), 109 (100), 81 (85).

Anal. Calcd for $C_8H_{11}Cl_3O_2$: C, 39.13; H, 4.52. Found: C, 39.10; H, 4.40.

After a few days, this fraction gave white crystals:[20] mp 98.5–99° (from *n*-hexane); ir (KBr) 3380 (OH), 1726 (C=O), 1160, 1120, 823, 795, and 734 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (d, 3, J = 6.5 Hz, CH_3), 1.60–2.70 (m, 5, C_3, C_4, C_5 H), 2.70–3.26 (m, 1, C_2 H), 3.63 (d, 1, J = 5.5 Hz, OH), and 4.71 ppm (q, 1, J = 5.5 and 1.5 Hz, >CHOH).

Anal. Calcd for $C_8H_{11}Cl_3O_2$: C, 39.13; H, 4.52. Found: C, 39.42; H, 4.21.

2-(2′,2′-Dichlorovinyl)-2-cyclopentenone (10a). To 70 ml of concentrated H_2SO_4 was added 7.0 g (0.03 mol) of **9a** at 0–5° with stirring. After being stirred for 20 hr, the mixture was poured into 200 ml of ice water. The organic layer was extracted with ether, washed with water, and dried over $MgSO_4$. Removal of the solvent left 3.9 g of a light brown oil which, on distillation, gave 1.2 g (23%)

of **10a:** bp 75–82° (3 mm); ir (neat) 1710 (C=O), 1620 (C=C), 808, and 790 cm^{-1}; nmr (CCl_4) δ 2.25–2.45 (m, 2, C_5 H), 2.60–2.84 (m, 2, C_4 H), 6.60 (s, 1, CCl_2=CH–), and 8.09 ppm (m, 1, C_3 H); mass spectrum (70 eV) *m/e* (rel intensity) 176 (65, M^+, 2 Cl), 141 (100, $M^+ - Cl$), 120 (51), 113 (58), 99 (43), 85 (39), 77 (54).

Anal. Calcd for $C_7H_6Cl_2O$: C, 47.49; H, 3.42. Found: C, 47.24; H, 3.59.

Synthesis of 10b from 9b. Hydroxy ketone **9b** was treated with concentrated H_2SO_4 in a way similar to the case of **10a.** It gave a 43% yield of **10b.** Ir and nmr spectra of this sample were identical with those of **10b** obtained in the preparation of **6b.**

5-Acetyl-7,7-dichloro-5-heptenoic Acid (14a). Procedure A. To a mixed solution of 1.3 g (0.01 mol) of **3a** and 1.7 g (0.015 mol) of freshly distilled dichloroacetaldehyde in 7 ml of dry THF was added 4.1 g (0.03 mol) of anhydrous potassium carbonate in several portions. After the mixture was stirred for 3 hr at room temperature, it was poured into 30 ml of water, washed with ether to remove neutral material, and then acidified with 10% HCl. The organic layer was extracted with ether several times, and the combined ethereal extract was dried over $MgSO_4$. Removal of the solvent left 1.44 g (36%[21]) of a light brown oil (**14a** of *ca.* 60% purity by thin layer chromatography[22]). A pure sample of **14a** was collected by preparative tlc for microanalysis and spectral determinations: R_f 0.30; ir (neat) 2300–3700 (COOH), 1710 (C=O), 1680 (C=O), and 1635 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.48–2.00 (m, 2, $-CH_2CH_2CH_2-$), 2.10–2.63 (m, 4, $-CH_2CH_2CH_2-$), 2.38 (s, 3, $COCH_3$), 6.58 and 6.98 (AB quartet, 2, J = 10 Hz, =$CHCHCl_2$), and 9.56 ppm (broad s, 1, COOH); mass spectrum (70 eV) *m/e* (rel intensity) 202 (98, $M^+ - HCl$, 1 Cl), 185 (39, 1 Cl), 168 (84), 167 (54), 142 (100), 129 (96), 108 (85), 95 (98), 84 (66), 43 (72).

Anal. Calcd for $C_9H_{12}Cl_2O_3$: C, 45.20; H, 5.06. Found: C, 44.99; H, 5.42.

Procedure B. Water was used as solvent. The procedure was analogous to that described in the above experiment. Removal of the solvent from the ethereal extract gave nearly pure **14a,** yield 59%. Spectral data (ir, nmr) were identical with those described above.

Methyl 5-Acetyl-7,7-dichloro-5-heptenoate (14b). Acid **14a** (0.41 g, 0.0017 mol) was esterified with diazomethane in the usual method. The crude product (0.37 g) was microdistilled to give 0.19 g of a clean oil which, on tlc analysis,[15] showed two spots at R_f values of 0.41[23] and 0.51. The compound with the R_f value of 0.51 was collected by preparative tlc and identified as **14b:** yield 28%; ir (neat) 1740 (C=O), 1680 (C=O), and 1640 cm^{-1} (C=C); nmr (CCl_4) δ 1.40–1.90 (m, 2, $-CH_2CH_2CH_2-$), 2.37 (s, 3, $COCH_3$), 2.10–2.60 (m, 4, $-CH_2CH_2CH_2-$), 3.66 (s, 3, $COOCH_3$), and 6.70 ppm (s, 2, =$CHCHCl_2$); mass spectrum (70 eV) *m/e* (rel intensity) 217 (52, $M^+ - Cl$, 1 Cl), 185 (100, $M^+ - Cl - CH_3OH$, 1 Cl), 181 (60, $M^+ - Cl - HCl$), 121 (80), 95 (60), 79 (82), 43 (84).

Anal. Calcd for $C_{10}H_{14}Cl_2O_3$: C, 47.45; H, 5.57. Found: C, 47.08; H, 5.53.

Oxidation of 14a with Potassium Permanganate. To a solution of 0.45 g (0.003 mol) of potassium permanganate in 6.1 ml of water was added in one portion a solution of 0.14 g (0.59 mmol) of **14a** in aqueous potassium hydroxide (0.053 g of KOH and 1.3 ml of water) at 35°. The mixture was stirred at 75° for 30 min, and then a solution of 0.32 ml of concentrated sulfuric acid in 0.98 ml of water was added. The mixture was heated on a steam bath for 15 min to coagulate the manganese dioxide, which was filtered while hot. The filtrate was evaporated to about 2 ml. The ethereal extract of the organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent the residue gave 0.058 g of white crystals. Tlc analysis[24] of this crystals showed two spots at R_f values of 0.21 and 0.31 in a ratio of 7:12. The compound with the R_f value of 0.21 was collected by preparative tlc and identified as succinic acid by comparison of its ir and nmr spectra with those of an authentic sample: mp 184–186° (lit.[25] mp 185°).

The compound with the R_f value of 0.31 was also collected by preparative tlc and identified as glutaric acid by comparison of its ir and nmr spectra with those of an authentic sample: yield 54%; mp 88–90° (from ether) (lit.[26] mp 89.5–91.5°).

Reaction of 2-Acetylcyclohexanone (15) with Chloral. To a mixed solution of 14.2 g (0.1 mol) of **15** and 14.7 g (0.1 mol) of chloral in 50 ml of dry THF was added 18.0 g (0.13 mol) of anhydrous potassium carbonate in several portions. The mixture was stirred for 12 hr at room temperature and then poured into 200 ml of water. After the mixture was acidified with 10% HCl, the organic layer was extracted with ether several times. The combined ethereal extract was washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was distilled to give 5.2 g of **15,** bp 62–67° (2 mm) [lit.[27] bp 97–98° (11 mm)], and 1.3 g of a fraction of bp 80–109° (2 mm). Tlc analysis[15] of the last fraction showed several spots and each of the components could not be separated. The same reaction was carried out in the similar way as described above, using dimethylsulfoxide as solvent. However, only the starting material **15** was recovered.

Treatment of 9a with Sodium Methoxide. To a suspension of 2.1 g (0.039 mol) of sodium methoxide in 20 ml of dry ether was added a solution of 1.5 g (0.0065 mol) of **9a** in 12 ml of ether at 0° with stirring. The color of the solution turned to brown during the course of addition, and the temperature rose to 13°. After the complete addition, the mixture was stirred for 30 min at room temperature and then acidified with 10% HCl. The organic layer was extracted with ether, washed with water, and dried over $MgSO_4$. After removal of the solvent, there was obtained the residue (0.21 g) which, on distillation, gave a solid. Its ir spectrum was identical with that of the starting material.

Registry No.—**3a,** 1670-46-8; **3b,** 52034-97-6; **6a,** 52034-99-8; **6b,** 52035-00-4; **7,** 52035-01-5; **8a,** 936-52-7; **8b,** 52124-24-0; **9a,** 52124-25-1; **9b,** 52124-26-2; **10a,** 52124-27-3; **10b,** 52124-28-4; **14a,** 52124-29-5; **14b,** 52124-30-8; **15,** 874-23-7.

References and Notes

(1) Preceding paper: A. Takeda, S. Tsuboi, and Y. Oota, *J. Org. Chem.*, **38,** 4148 (1973).
(2) Preliminary communication: A. Takeda, S. Tsuboi, F. Sakai, and M. Tanabe, *Tetrahedron Lett.*, 4961 (1973). Presented in part at the 27th Annual Meeting of the Chemical Society of Japan, Nagoya, Japan, Oct 12, 1972.
(3) A. Takeda and S. Tsuboi, *J. Org. Chem.*, **38,** 1709 (1973).
(4) This procedure to prepare α-alkylideneacetones from acetylacetone and α-halo aldehydes has been explored by one of us and his collaborator: A. Takeda, and T. Uno, to be published.
(5) A large amount of resinous material was produced. A trace of water in commercial grade THF is both essential and efficient for the reaction to occur.
(6) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen, London, 1968, p 24; it is known that the C=C frequency is observed usually at 1566 cm^{-1}.
(7) S. Borcic and J. D. Roberts, *J. Amer. Chem. Soc.*, **87,** 1056 (1965).
(8) A. E. Favorskii and V. N. Bozhovskii, *J. Russ. Phys. Chem. Soc.*, **50,** 582 (1920); *Chem. Abstr.*, **18,** 1476 (1924); M. Mousseron, R. Jacquier, and A. Fontaine, *Bull. Soc. Chim. Fr.*, **19,** 767 (1952).
(9) In addition to compound **7,** a moderate amount of nitrogen-free by-product melting at 83.5–84.5° was isolated. Its ir spectrum showed notable bands at 1780 (lactone C=O), 1705, 1632, and 1574 cm^{-1}. The identification of this material is still being elaborated.
(10) G. B. Brown, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 615.
(11) It may be suggested that a part of **14a** underwent a double bond shift to form 5-acetyl-7,7-dichloro-4-heptenoic acid.
(12) C. R. Hauser, F. W. Swamer, and B. I. Ringler, *J. Amer. Chem. Soc.*, **70,** 4023 (1948); P. J. Hamrick, Jr., C. F. Hauser, and C. R. Hauser, *J. Org. Chem.*, **24,** 583 (1959).
(13) W. Kemp, "Practical Organic Chemistry," McGraw-Hill, New York, N. Y., 1967, p 130.
(14) E. E. Blaise, and A. Koehler, *C. R. Acad. Sci.*, **148,** 1401 (1909).
(15) Developer, *n*-hexane–acetone (3:1 v/v).
(16) Any significant amount of nitrogen was not found.
(17) Developer, *n*-hexane–acetone (5:1 v/v).
(18) Total yield of **6b.** From the aqueous layer, an additional amount of **6b** (0.04 g) was obtained.
(19) This indicates the presence of cis and trans isomers (ca. 1:1).
(20) Either of the cis and trans isomers.
(21) Estimated as **14a.**
(22) Developer, *n*-hexane–acetone (2:1 v/v).
(23) This component was proved to be paraffin by ir spectrum.
(24) Developer, benzene–acetic acid–methanol (10:1:1 v/v/v).
(25) B. B. Allen, W. Wyatt, and H. R. Henze, *J. Amer. Chem. Soc.*, **61,** 843 (1939).
(26) J. English, Jr., and J. E. Dayan, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 499.
(27) W. Borsche, *Justus Liebigs Ann. Chem.*, **377,** 87 (1910).

The Chemistry of Carbanions. XXVI. The Synthesis of Certain γ-Alkenyl α,β-Unsaturated Ketones[1]

Herbert O. House,* Wei C. Liang, and Paul D. Weeks

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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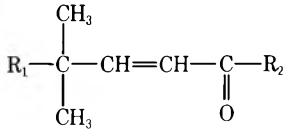
Alkylation of the α-carbon atom of isobutyraldehyde (3) was best accomplished by reaction of an alkyl halide with the corresponding lithium salt **8a** of the imine **7** rather than with the lithium enolate **6**. Reaction of the resulting alkylated aldehydes **16** with the ketone lithium enolate **20** afforded good yields of the aldols **21** which underwent acid-catalyzed dehydration to form the enones **22**. The enone **22d** was cyclized to the cyclopentane derivatives **23–25** under very mild conditions.

Our interest in the possible utilization of anion radicals **2** derived from unsaturated carbonyl compounds **1** as synthetic intermediates in carbon–carbon bond forming reactions led us to explore synthetic routes to enones of the type **1**. To examine possible synthetic applications involving intramolecular cyclization, we wanted enones **1** in which the γ substituent, R_1, contained unsaturation. Since



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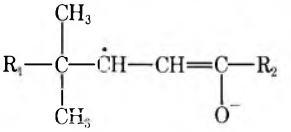
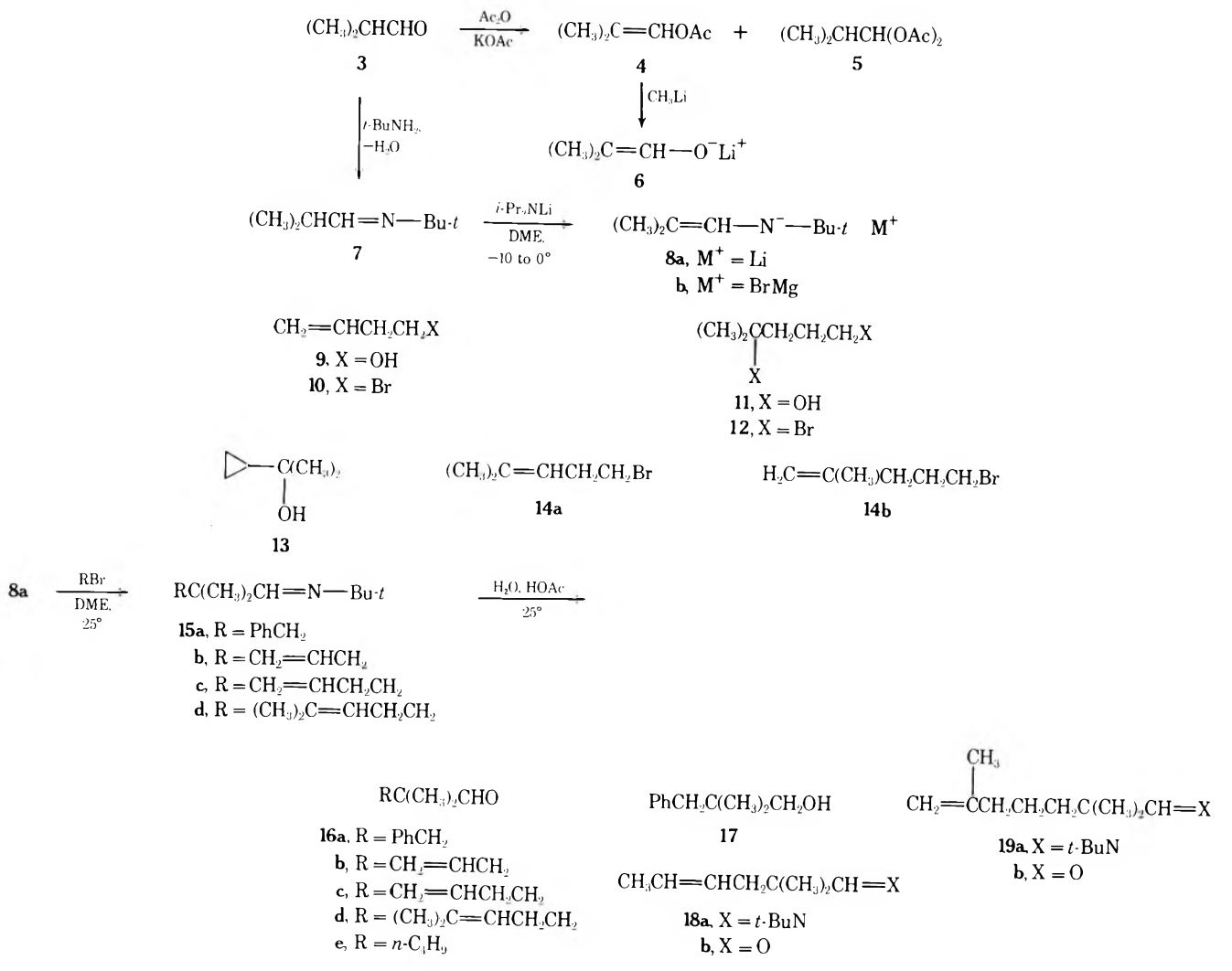


2

earlier studies[2] had indicated that relatively stable anion radicals **2** could be obtained from enones **1** when no hydrogen atoms were present at either the γ position (*i.e.*, $R_1 \neq H$) or the α′ position [*e.g.*, $R_2 = C(CH_3)_3$], we directed our attention to the synthesis of a series of enones **1** in which R_1 was an alkenyl group and R_2 was a *tert*-butyl group. This paper describes a satisfactory synthetic route to these substances.

Our synthetic plan required the alkylation of isobutyraldehyde (**3**) to form the aldehydes **16** (Scheme I) containing the desired alkenyl substituent R. Although isobutyraldehyde (**3**) has been successfully alkylated in moderate yields (15–75%) by treatment with a mixture of an alkyl ha-

Scheme I

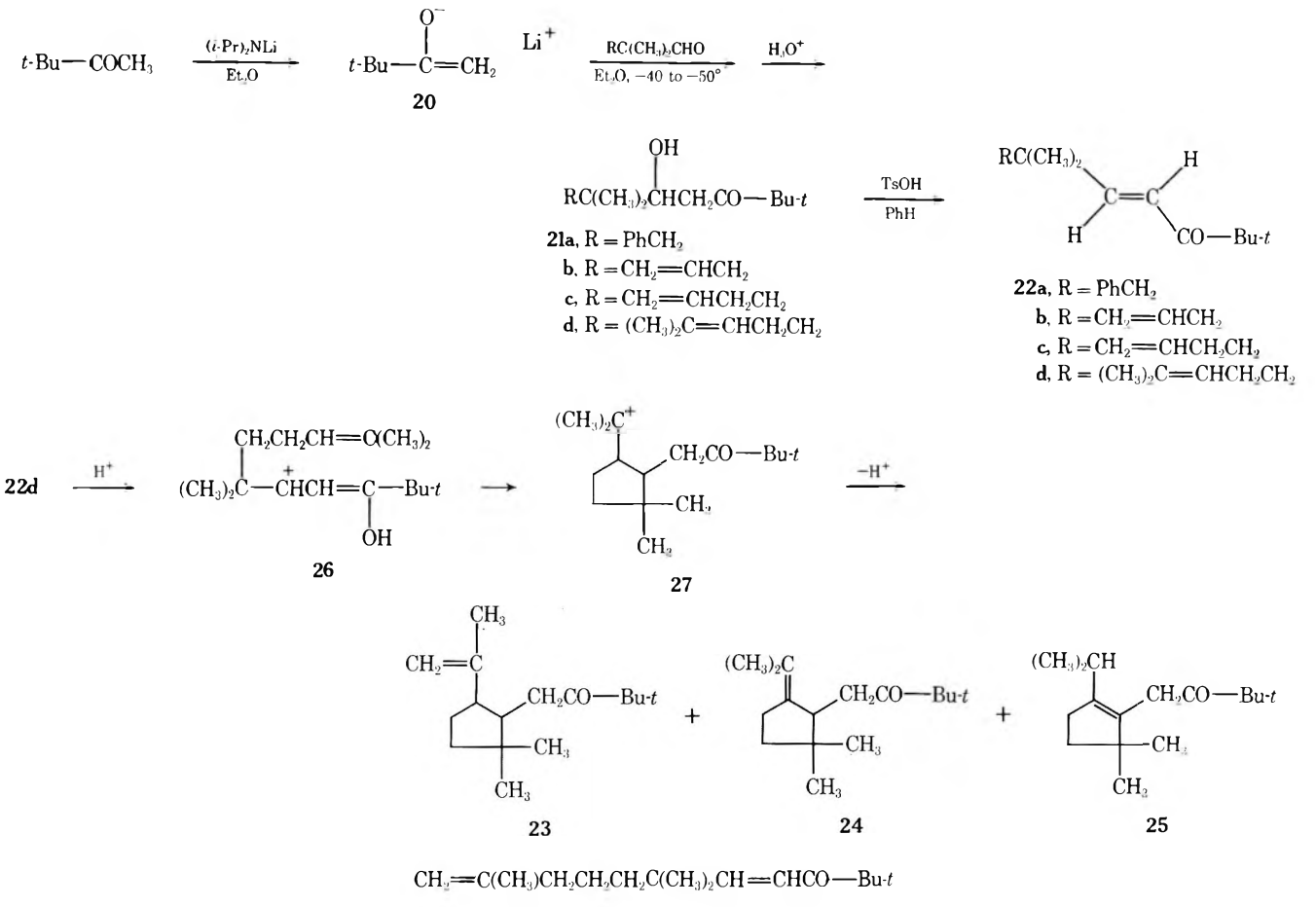


lide, aqueous 50% NaOH, and a tetrabutylammonium salt, this process was satisfactory only with very reactive alkyl halides such as methyl iodide or allylic or benzylic halides.[3] With less reactive alkyl halides, competing aldol condensation predominated.[3] We expected that competing aldol condensation might be minimized or eliminated if the aldehyde **3** was converted completely to its enolate anion **6** in an aprotic solvent before alkylation. Therefore, the lithium enolate **6** was generated in 1,2-dimethoxyethane (DME) solution either by adding the enol acetate **4** to 2 equiv of MeLi or by adding the aldehyde **3** to a cold (0–2°) solution of *i*-Pr_2NLi.[4] In each case, when the solution of the enolate **6** was treated with benzyl bromide, the desired alkylated product **16a** was accompanied by significant amounts of the alcohol **17** as well as higher boiling material. Alcohol and ester by-products were also produced along with the aldehyde **16b** when the lithium enolate **6** (from **4**) was treated with allyl bromide. Thus, we conclude that although the lithium enolates of aldehydes (*e.g.*, **6**) can be prepared in suitable aprotic media, the alkylation of these enolates is complicated by reaction of the alkylated aldehyde products **16** with the various bases (*e.g.*, **6**, *t*-BuO^-Li^+, *i*-$Pr_2N^-Li^+$) present in the reaction mixture to give the products of a Cannizzaro or a Tishchenko reaction.[5]

$$\underset{\mathbf{16}}{RC(CH_3)_2CHO} \xrightarrow{\text{base}} RC(CH_3)_2CH_2OH + RC(CH_3)_2CO_2^- + RC(CH_3)_2CH_2OCOC(CH_3)_2R$$

We, therefore, turned our attention to an alternative synthesis for the aldehydes **16** in which the imine **7** was converted to its anion **8** which would serve as the nucleophile in alkylation reactions. This alkylation procedure, as originally introduced by Stork and Dowd,[6] involved reaction of imines, such as **7**, with EtMgBr to form bromomagnesium salts (*e.g.*, **8b**). Subsequently, many workers have generated anions analogous to **8** employing various lithium salts as bases to form lithium salts such as **8a**.[7] In the present study we have compared the ease of converting the imine **7** to salt **8b** with EtMgBr in THF to the ease of converting it to the salt **8a** by reaction with *i*-Pr_2NLi in DME. The latter procedure, which forms the lithium salt **8a**, was clearly preferable. In the course of examining the formation of solutions of salt **8a** we also observed that this lithium salt **8a** attacks the solvent, DME, at temperatures above 30° to form the starting imine **7**, CH_3OLi, and $CH_2{=}CHOCH_3$. This same type of cleavage of DME with *i*-Pr_2NLi has been observed in the temperature range 0–10°.[4] Because of this solvent cleavage, the generation and use of the lithium salt **8a** was best accomplished by treatment of a cold (−10 to 0°) solution of *i*-Pr_2NLi in DME with the imine **7** followed by warming the solution to 10–20°. During the subsequent addition of alkyl halide the temperature of the exothermic reaction mixture was maintained in the range 20–30° to achieve reasonably rapid alkylation while avoiding extensive solvent cleavage. When the reaction mixture was hydrolyzed by addition of H_2O, the corresponding imines **15** could easily be isolated from the aqueous alkaline solutions. The imines **15** were best hydrolyzed to form the aldehydes **16** by stirring with a mixture of hexane and excess aqueous 1 *M* HOAc at 25°. The conditions, which give an aqueous medium of pH ~4 corresponding to the maximum rate of imine hydrolysis,[8] are to

Scheme II



EXPERIMENTAL SECTION[10]

Preparation of the Enol Acetate 4.[11] -- A solution of 216 g (3.00 mol) of isobutyraldehyde and 36 g (0.38 mol) of KOAc in 535.5 g (4.5 mol) of Ac_2O was refluxed for 12 hr, diluted with 1 l. of pentane, and washed with three 500-ml portions of water. The pentane solution was stirred at 25° with 250 ml of saturated aqueous $NaHCO_3$ solution containing excess $NaHCO_3$ for approximately 1 hr at which time all the excess Ac_2O had been hydrolyzed (ir analysis). The organic layer was dried, concentrated, and distilled to separate 146.7 g (42.8%) of the pure (glpc) enol acetate 4 as a colorless liquid, bp 124-126°, $n^{25}D$ 1.4201 [lit. bp 124-126°, $n^{25}D$ 1.4178;[12] bp 126°, $n^{20}D$ 1.4226[13]]; ir (CCl_4), 1750 (ester C=O) and 1690 cm^{-1} (enol C=C); nmr (CCl_4), δ 6.83 (1H, septuplet, J = 1.5 Hz, vinyl CH), 2.05 (3H, s, $COCH_3$), and 1.66 (6H, d, J = 1.5 Hz, CH_3); mass spectrum, m/e (relative intensity), 114 (M^+, 87), 72 (88), 57 (100), 43 (85), 41 (25), and 39 (27).

In an attempt to form the enol acetate 4 in an acid-catalyzed process,[14] a solution of 14.4 g (0.20 mol) of isobutyraldehyde and 50 ml (0.54 mol) of Ac_2O in 240 ml of CCl_4 was treated with 0.14 ml (ca 0.8 mmol) of aqueous 70% $HClO_4$ and the resulting solution was allowed to stand at 25° for 3 hr. The orange-brown reaction solution was diluted with 160 ml of pentane and stirred at 25° with 160 ml of saturated aqueous $NaHCO_3$ containing excess $NaHCO_3$ until the excess Ac_2O had been hydrolyzed. The resulting organic layer was dried, concentrated, and distilled to separate 21.8 g (63%) of the pure (glpc) acetate 5 as a colorless liquid, bp 89-90.5° (16 mm), $n^{25}D$ 1.4092 [lit.[15] bp 189°]; ir (CCl_4), 1765 cm^{-1} (ester C=O); nmr (CCl_4) δ 6.51 (1H, d, J = 5.0 Hz, $CH(OAc)_2$), 1.7-2.2 (7H, m, CH including a $COCH_3$ singlet at 2.01), and 0.95 (6H, d, J = 6.8 Hz, CH_3); mass spectrum, m/e (relative intensity), 131 (8), 115 (78), 103 (43), 71 (35), 58 (59), 44 (29), 43 (100), 42 (39), 41 (22), and 39 (22).

Preparation of the Imine 7.[6,16] -- Isobutyraldehyde (72 g or 1.0 mol), was added, dropwise and with stirring during 2 hr, to 73 g (1.0 mol) of t-$BuNH_2$. During the addition the temperature rose from 25° to 40° and an aqueous layer separated near the end of the addition. The organic layer was treated with 15 g of anhydrous K_2CO_3, stirred at 25° for 17 hr, and then decanted onto 12 g of BaO. After this mixture had been stirred at 25° for 10 hr, it was filtered and the organic filtrate was distilled to separate 88.3 g (70%) of the imine 7 as a colorless liquid, bp 56° (75 mm) [lit[16] bp 51-53° (83 mm), $n^{20}D$ 1.4078]; ir (CCl_4), 1675 cm^{-1} (C=N); nmr (CCl_4), δ 7.49 (1H, d, J = 4.5 Hz, CH=N), 2.0-2.6 (1H, m, CH), 1.10 (9H, s, t-Bu), and 1.03 (6H, d, J = 7 Hz, CH_3); mass spectrum, m/e (relative intensity), 127 (M^+, 6), 112 (25), 72 (16), 57 (100), 56 (15), 55 (18), and 41 (27).

Preparation of the Bromide 10. -- An ethereal solution of allylmagnesium bromide, from 242 g (2.00 mol) of allyl bromide, 53.5 g (2.2 g-atom) of Mg, and 1500 ml of Et_2O, was mixed with a slurry of 60.0 g (2.00 mol) of dry paraformaldehyde in 100 ml of Et_2O and the resulting mixture was refluxed with stirring for 6 hr.[17] After the usual isolation procedure, fractional distillation of the residual liquid through a 40-cm, spinning-band column separated 65.5 g (45.5%) of the unsaturated alcohol 9 as a colorless liquid, bp 112-113°, $n^{25}D$ 1.4195 [lit[18] bp 115° (770 mm), $n^{25}D$ 1.4182]; ir (CCl_4), 3620, 3360 (OH) and 1640 cm^{-1} (C=C); nmr (CCl_4), δ 4.8-6.2 (3H, m, vinyl CH), 3.97 (1H, broad, OH), 3.60 (2H, t, J = 7 Hz, CH_2-O), and 2.0-2.5 (2H, m, allylic CH_2); mass spectrum, m/e (relative intensity), 72 (M^+, 6), 57 (7), 43 (17), 42 (100), 41 (34), 39 (24), and 31 (74). The product exhibited a single glpc peak (silicone gum, No. SE-30, on Chromosorb P). To 24.0 g (89 mmol) of cold (-15°) PBr_3 was added, dropwise and with stirring during 2 hr with continuous cooling, a mixture of 12.2 g (170 mmol) of the alcohol 9 and 5.3 g (67 mmol) of pyridine. The resulting mixture, an orange slurry, was stirred at 25° for 2 hr and then distilled to separate 17.05 g (74.5%) of the bromide 10 as a colorless liquid, bp 96-99°, $n^{25}D$ 1.4665 [lit.[18] bp 99°, $n^{22}D$ 1.4625]; ir (CCl_4), 1640 cm^{-1} (C=C); nmr (CCl_4), δ 4.0-6.2 (3H, m, vinyl CH), 3.34 (2H, t, J = 6 Hz, addition long-range coupling also apparent, CH_2Br), and 2.3-2.8 (2H, m, allylic CH_2); mass spectrum, m/e (relative intensity), 137 (2), 136 (M^+, 4), 135 (2), 134 (M^+, 4), 55 (100), 41 (15), and 39 (18). Comparison of the nmr spectrum of this product with the spectrum of crotyl bromide established the absence of the isomeric bromide in our product.

Preparation of the Bromide 14a. -- A cold (-5°) solution of 0.29 mol of MeLi in 130 ml of Et_2O was treated, dropwise and with stirring during 1 hr, with 18.3 g (0.22 mol) of methylcyclopropyl ketone. The reaction mixture was stirred at 25° for 14 hr and then subjected to the usual isolation procedure to separate 13.4 g (61%) of the crude alcohol 13, bp 120-122°, that contained (glpc, Carbowax 20 M on Chromosorb P) the alcohol 13 (15.3 min, ca 94%) accompanied by the starting ketone (9.3 min, ca 6%). A solution of 13.4 g (0.134 mol) of the crude alcohol 13 in 30 ml of olefin-free pentane was stirred at 25° with 250 ml of aqueous 48% HBr for 25 min. Then an additional 100 ml of pentane was added and the organic layer was separated, washed successively with aqueous NaCl and aqueous $NaHCO_3$, and then dried and concentrated. Distillation of the residual liquid afforded 12.2 g (56%) of the bromo olefin 14, bp 91-93° (100 mm), $n^{25}D$ 1.4763 [lit.[20] bp 84-85° (84 mm), $n^{20}D$ 1.4758]; containing (nmr analysis) ca 96% of olefin 14a and ca 4% of olefin 14b.

To explore an alternative synthesis of the bromide 14a,[11] a cold (-5°) solution of 0.94 mol of MeLi in 500 ml of Et_2O was treated with 37.02 g (0.430 mol) of δ-butyrolactone and the resulting solution was allowed to warm to room temperature during 1 hr with stirring. Water (16.9 g or 0.94 mol) was added, dropwise and with stirring, the ethereal solution was decanted, and the residual semisolid was extracted with five 100-ml portions of Et_2O. The residual semisolid (containing most of the diol) was dissolved in 500 ml of H_2O and continuously extracted with Et_2O for 7 days. All of the Et_2O solutions were combined, dried, concentrated, and distilled to separate 26.12 g (51.1%) of the diol 11 as a colorless liquid, bp 97-98° (3 mm), $n^{25}D$ 1.4503 [lit.[21] bp 127-128° (22 mm), $n^{20}D$ 1.4449]; ir (CCl_4), 3600, and 3320 cm^{-1} (O-H); nmr (pyridine), δ 5.42 (2H, broad, OH), 3.7-4.0 (2H, m, CH_2O), 1.4-2.3 (4H, m, CH_2), and 1.33 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 103 (1), 85 (20), 59 (100), 43 (62), 42 (8), 41 (14), and 31 (17).

A solution of 11.8g (100 mmol) of the diol 11 in 5.4 g (68 mmol) of pyridine was added, dropwise with stirring and cooling, to 21.7 g (80 mmol) of cold (-5°) PBr_3. The reaction mixture was allowed to warm to 25°, diluted with 200 ml of Et_2O, and then treated with ice to destroy the excess PBr_3. The organic layer was washed successively with H_2O and with aqueous NaCl and then dried and concentrated. Distillation of the residual liquid (26.8 g) separated 19.1 g (78%) of the crude dibromide 12 as a colorless liquid, bp 98-104° (60 mm), $n^{25}D$ 1.4895 [lit.[20] bp 95° (20 mm), $n^{20}D$ 1.4990]. Although the product lacked ir absorption (CCl_4) in the 3- or 6-μ regions attributable to OH or C=O functions, the nmr spectrum (CCl_4) of the product exhibited weak nmr absorption in the region δ 4.6-5.3 attributable to the vinyl CH of unsaturated bromides 14 as well as nmr absorption attributable to the dibromide 12: δ 3.1-3.6 (2H, m, CH_2Br) and 1.5-2.8 (10H, m, CH_2 and a CH_3 singlet at 1.75). A mixture of 10.9 g (45 mmol) of the crude dibromide 12 and 3.6 g (46 mmol) of pyridine was slowly warmed to 100° and then heated at 100° for 20 min.[22] The mixture was distilled to separate 5.56 g (77%) of a fraction, bp 78-87° (90 mm), $n^{25}D$ 1.4758. An Et_2O solution of this fraction was washed successively with aqueous Na_2CO_3, with H_2O, and with aqueous NaCl, and then dried and concentrated. Distillation of the residual liquid (4.64 g) afforded 3.27 g (55%) of a mixture of the bromo olefins 14, bp 83.5-84.5° (85 mm), [lit.[20] for olefin 14a, bp 84-85° (84 mm), $n^{20}D$ 1.4758]. The nmr spectrum (CCl_4) of this mixture indicated the presence of ca 67% of the olefin 14a (vinyl multiplet at δ 5.0-5.3) and ca 33% of the olefin 14b (vinyl multiplet at δ 4.7-4.9). Our efforts to obtain a relatively pure sample of the bromo olefin 14a from this mixture were not successful.

Preparation of the Imine Salts 8. -- A cold (-55 to -57°) solution of i-Pr_2NLi, prepared from 57.8 mmol of MeLi, 5.85 g (57.8 mmol) of i-Pr_2NH, 3 mg of 2,2'-bipyridyl, and 30 ml of DME,[23] was treated with 6.60 g (52 mmol) of the imine 7. An aliquot of this cold solution was withdrawn and the nmr spectra of the aliquot was determined successively at temperatures of -10°, 0°, 25°, and 50°. The solution exhibited an nmr doublet (J = 4.5 Hz) at δ 7.55 characteristic of the imine 7 and a broad singlet at δ 6.38 attributable to the lithium derivative 8a. In addition, the solution at -10°, 0°, and 25° exhibited weak nmr peaks at δ 6.69, 6.57, and 6.45 that we attribute to part of the vinyl CH absorption of $CH_3OCH=CH_2$ from reaction of i-Pr_2NLi with the solvent.[24] The conversion of the imine 7 to the lithium derivative 8a was incomplete (nmr analysis) at -10° but was essentially complete at 0° and at 25°. As the solution was warmed to 50°, the extra nmr peaks, attributable to $CH_2=CHOCH_3$, increased in size with a corresponding decrease in the nmr peak attributable to the lithium reagent 8a. This observation indicates that attack of the lithium derivative 8a on DME becomes a serious competing reaction at temperatures above ca 30° and suggests that reaction solutions in DME employing the derivative 8a are best used within the temperature range 0 to 30°. When the remaining solution of i-Pr_2NLi in DME was warmed to 50° for 5 min and then stirred overnight at 25°, 1.0 g of CH_3OLi separated as a white precipitate. A solution of this precipitate in D_2O exhibited an nmr singlet at δ 3.37 (CH_3O) as well as weak singlets at δ 5.14 (OH) and 1.16.

To verify the location of the nmr peaks attributable to $CH_3OCH=CH_2$, a cold (-35 to -40°) solution of 50 mmol of i-Pr_2NLi in 50 ml of DME was warmed to 23° and allowed to stand for 15 hr. At this time the color of the 2,2-bipyridyl indicator was discharged indicating complete distruction of the i-Pr_2NLi. The nmr spectrum of this DME solution exhibited four low-field peaks at δ 6.69, 6.57, 6.45, and 6.33 attributable to the α-vinyl proton of $CH_3OCH=CH_2$.

To examine the formation of the bromomagnesium salt 8b,[6] a solution of 6.35 g (50 mmol) of the imine 7 and 50 mmol of EtMgBr in 44 ml of tetrahydrofuran (THF) was refluxed for 12 hr. However, the amount of EtH evolved (ca 100 ml) indicated that salt formation was incomplete. The nmr spectrum of this THF solution exhibited peaks of comparable intensity at δ 7.57 (doublet, J = 4Hz, CH=N of the imine 7) and at δ 6.30 (broad, singlet, CH=C of the BrMg salt 8b) also indicating that formation of the salt 8b was incomplete. The ratio of areas for these nmr peaks did not change after the solution had been kept at 25° for an additional three days.

Preparation of the Aldehyde 16a. A. From the Imine 7. -- A cold (-35°) solution of 50 mmol of i-Pr_2NLi in 35 ml of DME was treated with 6.36 g (50 mmol) of the imine 7. The resulting solution of the lithio imine 8a was warmed to 20° over a period of 1.3 hr and then treated, dropwise and with stirring during 12 min, with 8.55 g (50 mmol) of $PhCH_2Br$ while the temperature of the reaction mixture was kept in the range 20-40° by external cooling. When the addition was complete, the reaction mixture (a slurry containing solid LiBr) was stirred at 25° for 3.5 hr and then partitioned between aqueous NaCl and Et_2O. The ethereal solution was dried and then concentrated under reduced pressure. Distillation of the residual liquid (14.6 g) separated 1.25 g of forerun, bp 35-64° (0.45 mm), $n^{25}D$ 1.5292, and 8.25 g (ca 76%) of fractions, bp 65-69° (0.39-0.40 mm), $n^{25}D$ 1.4873-1.4883, containing (glpc, silicone fluid, SE-30, on Chromosorb P) primarily the imine 15a (ret. time 11.4 min) accompanied by several minor impurities (3.9 min, 4.9 min). A collected (glpc) sample of the imine 15a was obtained as a colorless liquid, $n^{25}D$ 1.4875; ir (CCl_4), 1665 and 1655 cm^{-1} (C=N); nmr (CCl_4), δ 7.47 (1H, s, CH=N), 7.0-7.2 (5H, m, aryl CH), 2.69 (2H, s, benzylic CH_2), 1.10 (9H, s, t-Bu), and 1.00 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 217 (M^+, 19), 202 (46), 147 (34), 91 (61), 57 (100), and 41 (23).

Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.45. Found: C, 83.01; H, 10.90; N, 6.04.

The optimum conditions for hydrolysis of the imine 15a were studied by stirring a mixture of a hexane solution of the imine 15a with various concentrations of aqueous HOAc.[25] After various reaction times and temperatures the organic solution was separated, washed successively with aqueous $NaHCO_3$, H_2O, and aqueous NaCl, and then dried and concentrated. Analysis (glpc, silicone gum, SE-30, on Chromosorb P) of the residual liquid determined the relative amounts of the imine 15a (retention time 7.2 min) and the aldehyde 16a (4.7 min) present. The following procedure was found to result in complete hydrolysis. A mixture of 16.33 g (75.2 mmol) of the imine 15a, 200 ml (200 mmol) of aqueous 1 M HOAc, and 80 ml of hexane was stirred at 22° under a nitrogen atmosphere for 2 hr and then saturated with NaCl and extracted with Et_2O. The organic solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. Distillation of the residual liquid (15.27 g) separated 11.4 g (ca 93%) of fractions, bp 56-59° (0.3-0.4 mm), containing (glpc, silicone gum, SE-30, on Chromosorb P) 96% or more of the aldehyde 16a (7.7 min) accompanied by a minor unidentified impurity (5.0 min).

A collected (glpc) sample of the pure aldehyde 16a was obtained as a colorless liquid, $n^{24}D$ 1.5072 [lit.[26] bp 57-58° (1 mm), $n^{20}D$ 1.5097], ir (CCl_4), 2800, 2770, 2690 (aldehyde, C-H), 1725 (strong), and 1700 cm^{-1}, (weak, C=O); uv (95% EtOH), a series of weak maxima (ε 157-227) in the region 242-267 mμ with a maximum at 293 mμ (ε 42); nmr (CCl_4), δ 9.48 (1H, s, CHO), 6.8-7.3 (5H, m, aryl CH), 2.70 (2H, s, benzylic CH), and 0.97 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 162 (M^+, 17), 92 (13), 91 (100), 65 (8), 55 (6), and 39 (6).

In an experiment where the intermediate imine 15a was not isolated, a solution of 50 mmol of the salt 8a in 40 ml of DME was treated with 8.54 g (50 mmol) of $PhCH_2Br$ (temperature of the mixture 7-60°). After the reaction mixture had been stirred at 24° for 21 hr, it was diluted with 60 ml of aqueous 10% HCl, refluxed for 2 hr and then cooled, saturated with NaCl and extracted with Et_2O. The ethereal solution was washed with aqueous NaCl, dried, and concentrated. Distillation of the residual liquid (9.83 g) afforded 5.56 (69%) of the aldehyde 16a, bp 55-57° (0.4-0.6 mm), $n^{25}D$ 1.5066, containing (glpc) one minor (ca 1%) lower boiling impurity. In a comparable experiment involving hydrolysis of the imine 15a for 1 hr, the initial neutral product isolated, bp 53-60° (0.3-0.4 mm), $n^{25}D$ 1.5083, amounted to only 2.73 g (34%). When the acidic aqueous layer was made basic (NaOH) and extracted with Et_2O, distillation of the organic extract afforded an additional 2.65 g (ca 32%) of product, bp 55-64° (0.8 mm), $n^{25}D$ 1.4986-1.5002, containing (glpc) mixtures of the aldehyde 16a and the unchanged imine 15a as well as minor amounts of lower boiling materials.

B. From the Lithium Enolate 6. -- To a cold (5-10°) solution of 50 mmol of MeLi and 3 mg of 2,2'-bipyridyl (an indicator) in 40 ml of DME was added, dropwise and with stirring during 25 min, 2.71 g (23.7 mmol) of the enol acetate 4.[27] The resulting pink (slight excess of MeLi) solution of the lithium enolate 6 was warmed to 25° and then treated with 8.55 g (50 mmol) of benzyl bromide. The reaction mixture was stirred at 30-40° (external cooling required initially) for 45 min and then a 25-ml aliquot of the mixture (total volume 67 ml) was partitioned between saturated aqueous $NaHCO_3$ and hexane. The remaining aqueous phase was extracted with ether and the combined organic extracts were dried and concentrated. Distillation of the residual liquid (1.20 g) separated 1.21 g of fractions, bp 88-96° (5 mm), and 0.49 of fractions, bp 61-89° (0.4 mm). The early fractions contained (glpc, silicone gum, SE-30, on Chromosorb P) varying amounts of $PhCH_2Br$ (5.3 min) and the aldehyde

16a (8.6 min) and later fractions contained these two components accompanied by the alcohol 17 (11.4 min) and bibenzyl (23.6 min). The estimated yields were: aldehyde 16a, 19%; alcohol 17, 7%; bibenzyl, 9%; and $PhCH_2Br$, 29% recovery. When the remainder of the reaction mixture was stirred for 20 hr at 25° and then subjected to the same isolation procedure, the crude product contained (ir and nmr analysis) none of the desired aldehyde 16a. From a comparable reaction employing a reaction time of 1 hr at 25-41°, and an additional 30 min at reflux, the estimated yields were: aldehyde 16a, 12%; alcohol 17, 20%; bibenzyl, 23%; and $PhCH_2Br$, 32% recovery. When the reaction time was shortened to 2.5 min at 10-25°, only $PhCH_2Br$ (ca 80% recovery) and bibenzyl (ca 10%) were found. Collected (glpc) samples of bibenzyl and the aldehyde 16a were identified with authentic samples by comparison of ir and nmr spectra and glpc retention times. A collected (glpc) sample of the alcohol 17 was obtained as a colorless liquid [lit.[27] mp 33-35°, bp 120-124° (14 mm)]: ir (CCl_4), 3630 and 3390 cm^{-1} (OH); nmr (CCl_4), δ 7.0-7.4 (5H, m, aryl CH), 3.27 (2H, s, CH_2O), 2.93 (1H, s, OH), 2.55 (2H, s, benzylic CH_2), and 0.84 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 164 (M^+, 15), 92 (92), 91 (100), 73 (25), 55 (22), and 43 (19).

Since the major difficulty in this reaction appeared to arise from a Cannizzaro reaction of the initially formed aldehyde 16a caused by the bases (t-BuOLi and 6) present in the reaction mixture, we also examined the preparation of the lithium enolate by direct reaction of isobutyraldehyde with i-Pr_2NLi. To a cold (0-2°) solution of 50 mmol of i-Pr_2NLi in 40 ml of DME was added, dropwise and with stirring and cooling during 20 min, a solution of 6.10 g (63 mmol) of isobutyraldehyde in 5 ml of DME.[23] The resulting pink (slight excess of i-Pr_2NLi) solution was warmed to 21°, stirred at 21-23° for 30 min, and then treated with 8.54 g (50 mmol) of $PhCH_2Br$. The resulting mixture was stirred at 23-35° for 30 min and then poured into 40 ml of cold aqueous 10% HCl, saturated with NaCl, and extracted with Et_2O. The organic solution was washed successively with aqueous 5% HCl and with aqueous NaCl and then dried and concentrated. Distillation of the residual liquid (10.5 g) separated 7.50 g of fractions, bp 35-98° (0.3-0.4 mm), containing (glpc) various amounts of $PhCH_2Br$, aldehyde 16a, and alcohol 17 as well as other minor unidentified products. The estimated yields were: aldehyde 16a, 40%; alcohol 17, 6%; and $PhCH_2Br$, 31% recovery.

Preparation of the Aldehyde 16b. A. From the Enamine.[11] Following a previous procedure,[28] the pyrrolidine enamine of isobutyraldehyde was prepared in 71% yield: bp 93-95° (100 mm), $n^{25}D$ 1.4724 [lit. 43-44° (12 mm),[28a] $n^{20}D$ 1.4741[28b]]. Reaction of 15.1 g (125 mmol) of allyl bromide (bp 67-70°) with 15.6 g (125 mmol) of this enamine for 20 hr at ambient temperature followed by hydrolysis with aqueous 2 M HCl afforded 4.112 g (29%) of the unsaturated aldehyde 16b as a colorless liquid, bp 123-125°, $n^{25}D$ 1.4189-1.4190 [lit.[28] bp 124-125°, $n^{20}D$ 1.4203]: ir (CCl_4), 2800, 2700 (aldehyde CH), 1730 (C=O), 1640 (C=C), 995 and 920 cm^{-1} (CH=CH_2): nmr (CCl_4), δ 9.47 (1H, s, CHO), 4.8-6.1 (3H, m, vinyl CH), 2.19 (2H, d of t, J = 7.2 and 0.9 Hz, allylic CH_2), and 1.03 (6H, s, CH_3); mass spectrum m/e (relative intensity), 112 (M^+, 4), 97 (32), 94 (41), 84 (25), 83 (75), 70 (75), 69 (64), 67 (27), 56 (91), 55 (100), 53 (30), 43 (79), 42 (31), 41 (79), and 39 (61).

An attempt to prepare the aldehyde 16b by reaction of the lithium enolate 6 (from enol acetate 4) with allyl bromide in DME afforded a complex mixture that contained (ir and glpc) the aldehyde 16b accompanied by alcohol and ester products as well as other unidentified materials.

B. From the Imine 7. -- A solution of 100 mmol of the salt 8a in 90 ml of DME was treated with 12.1 g (100 mmol) of allyl bromide during 25 min while the temperature was maintained in the range 19-40° by use of external cooling. After the mixture had been stirred at 23° for 12 hr and then subjected to the previously described isolation procedure, distillation separated 12.5 g (75%) of the crude imine 15b as colorless liquid fractions, bp 24-56° (10-14 mm), $n^{25}D$ 1.4210-1.4265. The later fractions from the distillation, bp 53-56° (14 mm), $n^{25}D$ 1.4260-1.4265, contained (glpc, TCEP on Chromosorb P) the pure imine 15b (ret. time 10.4 min). An analytical sample of the imine 15b was collected (glpc): ir (CCl_4), 1665 (C=N), 1640 (C=C), 1000, and 925 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 7.42 (1H, s, CH=N), 4.8-6.0 (3H, m, vinyl CH), 2.12 (2H, d, J = 7 Hz, allylic CH_2), 1.10 (9H, s, t-Bu), and 0.96 (6H, s, CH_3); mass spectrum m/e (rel. intensity), 167 (M^+, 2), 152 (16), 112 (40), 111 (15), 96 (38), 84 (11), 70 (17), 57 (100), 55 (27), and 41 (32).

Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found: C, 78.96; H, 12.65; N, 8.38.

Use of the previously described hydrolysis procedure with 6.68 g (40 mmol) of the imine 15b, 30 ml of hexane, and 100 ml (30 mmol) of aqueous 1 M HOAc afforded 7.35 g of low-boiling fractions, bp 30-42° (135 mm), and 3.61 g (80%) of the crude aldehyde 16b as a colorless liquid, bp 79-81° (135 mm), $n^{25}D$ 1.4140. This product exhibited one major glpc peak (TCEP on Chromosorb P) corresponding to the aldehyde 16b (ca. 86%, 20.2 min) accompanied by minor unidentified components (9.6 min, 23.2 min). The product was identified with the previously described sample of the aldehyde 16b by comparison of ir spectra.

Preparation of the Aldehyde 16c. -- A solution of 50 mmol of the salt 8a in 35 ml of DME was treated with 6.75 g (50 mmol) of the bromo olefin 10 during 15 min while the reaction temperature was kept at 25-39°. The resulting mixture was stirred at 25° for 16 hr and then subjected to the previously described isolation procedure to separate 6.50 g (72%) of the crude imine 15c as colorless liquid fractions, bp 63-69° (15 mm), $n^{25}D$ 1.4308-1.4310. Analysis [glpc, TCEP on Chromosorb P] of this crude product indicated the presence of the imine 15c (ret. time 11.4 min) accompanied by minor amounts of two impurities (10.8 and 12.6 min) believed to be isomeric imines 18a. These impurities were partially removed by collection (glpc, TCEP column) to give a sample of the partially purified imine 15c as a colorless liquid, $n^{25}D$ 1.4310: ir (CCl_4), 1663 (C=N), 1638 (C=C), 995, and 920 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 7.40 (1H, s, CH=N), 4.7-6.1 (3H, m, vinyl CH), 1.2-2.2 (4H, m, CH_2), 1.10 (9H, s, t-Bu), and 1.00 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 181 (M^+, 0.5), 166 (5), 127 (35), 112 (31), 71 (28), 57 (100), 55 (32), and 41 (32).

Hydrolysis of 5.70 g (31.4 mmol) of the crude imine 15c with 30 ml of hexane and 100 ml of aqueous 1 M HOAc yielded 2.96 g (75%) of the crude aldehyde 16c as a colorless liquid, bp 63-64° (17 mm), $n^{25}D$ 1.4250. This product contained (glpc, TCEP on Chromosorb P) primarily the aldehyde 16c (ret. time 33.8 min) accompanied by a minor impurity (ca. 10%, 29.0 min) thought to be the isomeric aldehyde 18b. A collected (glpc sample of the product thought to be aldehyde 18b was obtained as a colorless liquid; ir (CCl_4), 2810, 2780, 2700 (aldehyde CH), 1720 (C=O), and 982 cm^{-1} (trans CH=CH): mass spectrum, m/e (relative intensity), 126 (M^+, 73), 111 (66), 108 (52), 97 (37), 83 (62), 72 (75), 70 (60), 69 (70), 57 (75), 56 (80), 55 (100), 54 (42), 53 (57), 43 (84), 41 (75), and 39 (68).

A collected (glpc) sample of the aldehyde 16c was obtained as a colorless liquid, $n^{25}D$ 1.4255: ir (CCl_4), 2810, 2780, 2700 (aldehyde CH), 1725 (C=O), 1640 (C=C), 1000, and 925 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 9.43 (1H, s, CHO), 4.7-6.2 (3H, m, vinyl CH), 1.3-2.2 (4H, m, CH_2), and 1.04 (6H, s, CH_3); mass spectrum m/e (relative intensity), 126 (M^+, <1), 97 (9), 82 (13), 72 (55), 69 (9), 57 (15), 56 (15), 55 (100), 43 (24), 41 (16), and 39 (15).

Anal. Calcd for $C_9H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.14; H, 11.20.

Preparation of the Aldehyde 16d. -- A solution of 50 mmol of the salt 8a in 50 ml of DME was treated with 8.2 g (50 mmol) of the bromide 14a during 15 min and the resulting mixture was stirred at 25° for 15 hr. After following the previously described isolation procedure, distillation separated 1.2 g of a low-boiling fraction, bp 30-59° (15 min), containing (glpc, TCEP on Chromosorb P) the bromide 14a (ca. 75%, ret. time 18.5 min), the imine 15d (ca. 9%, 20.1 min), and several minor unidentified components (5-6 min). Subsequent distillation fractions amounted to 1.4 g, bp 61-108° (15 mm), containing (glpc) the bromide 14 (ca 42%) and the imine 15d (ca 58%) and 5.9 g, bp 109-110° (15 mm), containing (glpc) the bromide 14a (ca 5%) and the imine 15d (ca 95%). Thus, the total yield of imine 15d was ca 59%. A pure sample of the imine 15d was collected (glpc) as a colorless liquid, $n^{25}D$ 1.4421: ir (CCl_4), 1665 cm^{-1} (C=N); nmr (CCl_4), δ 7.40 (1H, s, CH=N), 4.6-5.3 (1H, m, vinyl CH), 1.2-2.2 (10H, m, CH_2 and allylic CH_3), 1.12 (9H, s, t-Bu), and 0.98 (6H, s, CH_3C); mass spectrum, m/e (rel. intensity), 209 (M^+, 1), 194 (2), 127 (100), 112 (57), 71 (54), and 49 (36).

Anal. Calcd for $C_{14}H_{27}N$: C, 80.31; H, 13.00; N, 6.69. Found: C, 80.28; H, 12.96; N, 6.73.

Hydrolysis of 4.63 g (22 mmol) of the imine 15d with 25 ml of hexane and 75 ml of aqueous 1 M HOAc yielded 2.87 g (82%) of the aldehyde 16d, bp 81-84° (15 mm), which showed a single glpc peak (silicone SE-30 on Chromosorb P, ret. time 15.2 min). A collected (glpc) sample of the aldehyde 16d was obtained as a colorless liquid, $n^{25}D$ 1.4417; ir (CCl_4), 2810, 2785, 2705 (aldehyde CH) and 1727 cm^{-1} (C=O); nmr (CCl_4), δ 9.43 (1H, s, CHO), 4.8-5.3 (1H, m, vinyl CH), 1.2-2.2 (10H, m, CH_2 and allylic CH_3), and 1.02 (6H, s, CH_3); mass spectrum, m/e (rel. intensity), 154 (M^+, 1), 83 (81), 82 (82), 72 (56), 69 (75), 67 (48), 56 (35), 55 (47), and 41 (100).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.88; H, 11.76.

Preparation of the Aldehyde 16e. -- A cold (6°) solution of 50 mmol of the lithio derivative 8a in 40 ml of DME was treated with 6.85 g (50 mmol) of n-BuBr and the resulting mixture, which initially warmed to ca 50°, was stirred at 23° for 19 hr. The mixture was diluted with 60 ml of aqueous 10% HCl, refluxed for 1.5 hr, and then subjected to the previous isolation procedure to separate 2.94 g of distillate, bp 80-82° (20-80 mm), that contained (glpc, silicone gum, SE-30, on Chromosorb P) the desired aldehyde 16e (10.8 min, estimated yield 43%) accompanied by several minor, more rapidly eluted components. A collected (glpc) sample of the pure aldehyde 16e was obtained as a colorless liquid, $n^{25}D$ 1.4121 [lit.[30] bp 40° (5 mm), $n^{25}D$ 1.4140]: ir (CCl_4), 2805, 2790, 2700 (aldehyde CH), and 1725 cm^{-1} (C=O); nmr (CCl_4), δ 9.38 (1H, s, CHO), 1.1-1.5 (6H, m, CH_2), and 0.8-1.1 (9H, m, CH_3 including a singlet at 1.00); mass spectrum m/e (relative intensity), 128 (M^+, <1), 99 (48), 71 (100), 57 (97), 55 (57), 43 (94), 41 (97), and 39 (53).

Preparation of the Ketols 21.[5] A. Ketol 21a. -- To a cold (-30°) solution of i-Pr_2NLi, from 10.0 mmol of MeLi, 1.11 g (11 mmol) of i-Pr_2NH, 3 mg of 2,2'-bipyridyl, and 10 ml of Et_2O, was added dropwise and with stirring during 1 min, 1.00 g (10 mmol) of pinacolone. The resulting brown solution was stirred at -50 to -60° for 0.5 hr and then 1.62 g (10 mmol) of the aldehyde 16a was added, dropwise and with stirring during 1 min. The resulting light yellow solution was stirred at -35° for 15 min and then 40 ml of ice cold aqueous 1 M HCl was added. The mixture was saturated with NaCl 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 crude ketol 21a amounted to 2.50 g (96%) of white solid, mp 59.5-65°, which exhibited a single spot (R_f 0.65) on tlc analysis [silica coating with Et_2O-hexane (1:1 v/v) as eluent]. Recrystallization from hexane afforded the pure ketol 21a as white leaflets, mp 70-70.5°; ir (CCl_4), 3450 (associated OH) and 1690 cm^{-1} (C=O, H-bonded); uv (95% EtOH), a series of weak maxima (ε 261 or less) in the region 242-268 mμ with a maximum at 285 mμ (ε 19); nmr (CCl_4), δ 7.0-7.3 (5H, m, aryl CH), 3.62 (1H, d of d, J = 8.6 and 3 Hz, CH-O), 3.20 (1H, broad, OH, exchanged with D_2O), 2.3-3.0 (4H, m, CH_2CO and benzylic CH_2), 1.10 (9H, s, t-Bu), 0.89 (3H, s, CH_3), and 0.80 (3H, s, CH_3); mass spectrum, m/e (relative intensity), 244 (27), 187 (68), 163 (63), 162 (93), 159 (65), 147 (70), 145 (62), 133 (54), 119 (67), 117 (56), 105 (74), 100 (61), 92 (66), 91 (100), 69 (64), 57 (73), and 43 (61).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 77.82; H, 9.99. Found: C, 77.90; H, 9.97.

B. Ketol 21b. -- When the same procedure was followed with 23.9 mmol of i-Pr_2NLi, 15 ml of Et_2O, 2.39 g (23.9 mmol) of pinacolone, and 3.13 g of the crude aldehyde 16b (containing 23.9 mmol of 16b), the residual colorless liquid product (4.96 g) contained [tlc, silica coating, eluent Et_2O-hexane (1:1 v/v)] primarily the aldol 21b (R_f 0.52) accompanied by a minor unidentified component (R_f 0.22). A 20.6-mg portion was chromatographed [acid-washed silicic acid, Et_2O-hexane (1:4 v/v) eluent] to separate 19.2 mg of the major component, the ketol 21b, as a colorless liquid, $n^{25}D$ 1.4525: ir (CCl_4), 3540 (associated OH), 1695 (C=O, H-bonded), 1635 (C=C), 1005, and 925 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 4.8-6.2 (3H, m, vinyl CH), 3.65 (1H, d of d, J = 9 and 3 Hz, CH-O), 2.95 (1H, broad, exchanged with D_2O, OH), 1.9-2.7 (4H, m, CH_2CO, and allylic CH_2), 1.13 (9H, s, t-Bu), 0.89 (3H, s, CH_3), and 0.86 (3H, s, CH_3); mass spectrum m/e (relative intensity), 194 (<1), 153 (2), 137 (8), 100 (17), 85 (10), 57 (100), 56 (20), 55 (70), 43 (38), 41 (90), and 39 (22).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.57; H, 11.43.

An attempt to purify the crude ketol 21b by short-path distillation afforded a colorless liquid, bp 35-42° (15 mm), $n^{25}D$ 1.4519, which contained (tlc) primarily the ketol 21b (R_f 0.64), accompanied by two minor unidentified materials (R_f 0.50 and 0.12).

C. Ketol 21c. -- The same procedure with 10 mmol of i-Pr_2NLi, 10 ml of Et_2O, 1.00 g (10 mmol) of pinacolone, and 1.26 g (10 mmol) of the aldehyde 16c yielded 2.08 g (92%) of the crude ketol 21c as a colorless liquid. This crude product contained [tlc, silica gel coating with an Et_2O-hexane eluent (1:1 v/v)] primarily the ketol 21c (R_f 0.66) accompanied by several minor unidentified components (R_f 0.77, 0.43, and 0.16). A 1.268-g sample of this crude product was chromatographed on 100 g of acid-washed silicic acid employing an ether-hexane mixture (1:5 v/v) as the eluent. The intermediate fractions contained (tlc) the partially purified ketol 21c isolated as a colorless liquid, $n^{25}D$ 1.4537: ir (CCl_4), 3620 (shoulder), 3540 (OH), 1695 (H-bonded C=O), 1640 (C=C), 1000, and 920 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 4.7-6.2 (3H, m, vinyl CH), 3.71 (1H, d of d, J = 9 and 3 Hz, CH-O), 3.11 (1H, broad, OH), 1.2-2.6 (6H, m, CH_2), 1.12 (9H, s, t-Bu), 0.89 (3H, s, CH_3), and 0.87 (3H, s, CH_3).

D. Ketol 21d. -- Use of this procedure with 17.5 mmol of i-Pr_2NLi, 10 ml of Et_2O, 1.75 g (17.5 mmol) of pinacolone, and 2.70 g (17.5 mmol) of the aldehyde 16d yielded 4.3 g (97%) of the crude ketol 21d as a white solid. The nmr spectrum (CCl_4) of this crude product exhibited a multiplet at δ 4.8-5.3 (vinyl CH of 21d) as well as a weak multiplet at δ 4.5-4.8 probably attributable to some of the isomer 28 with a terminal double bond. Repeated recrystallization from hexane separated the pure ketol 21d as white needles, mp 36-36.5°: ir (CCl_4), 3540 (broad, OH) and 1690 cm^{-1} (H-bonded C=O); nmr (CCl_4), δ 4.8-5.3 (1H, m, vinyl CH), 4.68 (1H, d of D, J = 3.8 and 8.2 Hz, carbinol CH), 3.12 (1H, broad, OH), 2.3-2.8 (2H, m, CH_2CO), 1.8-2.2 (2H, m, allylic CH_2), 1.68 (3H, broad, s, allylic CH_3), 1.62 (3H, broad s, allylic CH_3), 1.2-1.6 (2H, m, CH_2), 1.14 (9H, s, t-Bu), 0.99 and 0.96 (6H, two partially resolved singlets, CH_3); mass spectrum, m/e (rel. intensity), 166 (16), 165 (21), 100 (18), 83 (57), 82 (56), 72 (34), 69 (70), 67 (40), 57 (100), 56 (30), 55 (36), 43 (36), and 41 (25).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.53; H, 11.89. Found: C, 75.63; H, 11.92

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Preparation of the Enones 22. A. Enone 22a. -- A solution of 2.50 g (9.5 mmol) of the crude ketol 21a and 131 mg (0.67 mmol) of p-TsOH in 45 ml of PhH was boiled until 2 ml of the PhH-H_2O azeotrope had been distilled and then the solution was cooled and washed successively with aqueous NaCl, with aqueous $NaHCO_3$, and with aqueous NaCl. After the organic solution had been dried and concentrated, the residual liquid (2.37 g) was distilled under reduced pressure in a short-path still to separate 1.90 g (*ca* 90%) of the crude trans-enone 22a as a colorless liquid, $n^{25}D$ 1.5052, bp 162-164° (8 mm), which exhibited one major glpc (silicone gum, SE-30, on Chromosorb P) peak corresponding to the enone 22a (7.8 min) accompanied by a minor, more rapidly eluted impurity (1.1 min). A collected (glpc) sample of the pure enone 22a was obtained as a colorless liquid, $n^{25}D$ 1.5055. The product was also purified by crystallization from hexane at Dry Ice temperature to separate the enone 22a as white needles, mp 34-34.5°; ir (CCl_4), 1685 (conjugated C=O), 1620 (C=C), and 980 cm^{-1} (trans CH=CH); uv max (95% EtOH), 230 mμ (ε 11,200); nmr (CCl_4), δ 6.7-7.3 (6H, m, aryl CH and 1 vinyl CH), 6.13 (1H, d, J = 15.5 Hz, vinyl CH), 2.63 (2H, s, benzylic CH_2), and 1.04 (15H, s, t-Bu and CH_3); mass spectrum, m/e (relative intensity), 244 (M^+, 32), 187 (91), 159 (90), 145 (94), 91 (100), 69 (59), 57 (74), and 43 (40).

Anal. Calcd for $C_{18}H_{24}O$: C, 85.55; H, 9.90. Found: C, 83.67; H, 9.86.

B. Enone 22b. -- After a solution of 2.12 g (10 mmol) of the crude ketol 21b and 132 mg (0.7 mmol) of p-TsOH in 90 ml of PhH was boiled for 10 min, during which time 15 ml of distillate was removed, application of the usual isolation procedure separated 2.46 g of residual colorless liquid. A 963-mg. portion of the crude product was distilled to separate 733 mg (96%) of colorless liquid, bp 44° (25 mm), $n^{25}D$ 1.4617. This material exhibited one major glpc peak (silicone gum, SE-30, on Chromosorb P) corresponding to the enone 22b (13.2 min). A collected (glpc) sample of the pure enone 22b was obtained as a colorless liquid, $n^{25}D$ 1.4567; ir (CCl_4), 1688 (conjugated C=O), 1640 (C=C), 1620 (conjugated C=C), 990, and 900 cm^{-1} (CH=CH_2 and trans CH=CH); uv max (95% EtOH), 230 mμ (ε 11,800), and 321 mμ (ε 63); nmr (CCl_4), δ 6.81 (1H, d, J = 15.5 Hz, vinyl CH), 6.32 (1H, d, J = 15.5 Hz, vinyl CH), 4.7-6.0 (3H, m, vinyl CH), 2.15 (2H, d, J = 6.5 Hz, further partially resolved splitting apparent, allylic CH_2), 1.14 (9H, s, t-Bu), and 1.09 (6H, s, CH_3); mass spectrum, m/e (relative intensity), 194 (M^+, 1), 153 (22), 137 (60), 109 (55), 95 (32), 85 (18), 69 (28), 67 (37), 57 (100), and 41 (48).

Anal. Calcd for $C_{11}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.49; H, 11.43.

C. Enone 22c. -- A solution of 717 mg (3.2 mmol) of the crude ketol 21c and 44.8 mg (0.24 mmol) of p-TsOH in 30 ml of PhH was refluxed for 10 min and then subjected to the usual isolation procedure. Distillation of the crude liquid product (710 mg) in a short-path still separated 578 mg (87%) of the enone 22c as a colorless liquid, bp 91-96° (8 mm) that contained (glpc, silicone SE-30 on Chromosorb P) primarily the enone 22c (ret. time 19.1 min) accompanied by a minor unidentified impurity (4.7 min). A collected (glpc) sample of the enone 22c, $n^{25}D$ 1.4589, was used for characterization: ir (CCl_4), 1635 (conjugated C=O), 1640 (C=C), 1620 (conjugated C=C), 995, and 925 cm^{-1} (CH_2=CH and trans CH=CH); nmr (CCl_4), δ 6.80 (1H, d, J = 15.5 Hz, vinyl CH), 6.32 (1H, d, J = 15.5 Hz, vinyl CH), 5.7-6.1 (3H, m, CH=CH_2), 1.2-2.3 (4H, m, CH_2), 1.12 (9H, s, t-Bu), and 1.08 (6H, s, CH_3); uv max (95% EtOH), 230 mμ (ε 11,800), and 321 mμ (ε 64); mass spectrum, m/e (rel. intensity), 208 (M^+, 12), 193 (5), 151 (100), 123 (31), 109 (90), 107 (41), 95 (25), 81 (71), 69 (68), 67 (46), 57 (95), 55 (47), 43 (24), 41 (85), and 39 (20).

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Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 81.06; H, 11.80.

In an alternative purification procedure, 500 mg of the crude enone 22c was repeatedly crystallized from hexane at Dry Ice temperatures to separate the enone 22c as a colorless crystalline solid that remained solid when stored at -8°.

D. Enone 22d. -- A solution of 0.54 g (2.1 mmol) of the crude aldol 21d and 5 mg (0.003 mmol) of TsOH in 20 ml of PhH was refluxed for 10 min and then subjected to the usual isolation procedure. The nmr spectrum (CCl_4) of the crude product indicated the presence of both the desired enone 22d (*ca* 84%, vinyl CH at δ 4.8-5.3) and a second minor component believed to be the double bond isomer 28 [*ca* 16%, vinyl CH at δ 4.5-4.8; ir (CCl_4), 1680 (conjugated C=O), 1620 (C=C), and 900 cm^{-1} (C=CH_2)]. When the same reaction was repeated with 230 mg of the pure aldol 21d, the crude enone product (204 mg) again contained (nmr analysis) a mixture of *ca* 83% of the enone 22d and *ca* 17% of a contaminant believed to be enone 28. A 200-mg sample of the crude enone was partially purified by preparative tlc employing a silica gel GF-254 coating with an Et_2O-hexane mixture (3:97 v/v) as the eluent. This procedure separated 130 mg of a fraction (R_f 0.5) of colorless liquid that contained (nmr analysis) primarily the enone 22d accompanied by a small amount of the double bond isomer 28. Repeated recrystallization of this material from hexane at Dry Ice temperatures separated 80 mg of the pure enone 22d as white needles, mp 22°; ir (CCl_4), 1690 (conjugated C=O), 1620 (conjugated C=C), and 985 cm^{-1} (trans CH=CH); uv max (95% EtOH), 229 mμ (ε 13,300) and 323 mμ (ε 68); nmr (CCl_4), δ 6.84, 6.39 (2H, AB pattern with J = 16 Hz, trans CH=CH), 4.8-5.3 (1H, m, vinyl CH), 1.2-2.2 (10H, m, including two broad peaks at 1.68 and 1.58, CH_2 and allylic CH_3), 1.14 (9H, s, t-Bu), and 1.08 (6H, s, CH_3); mass spectrum, m/e (rel. intensity), 236 (M^+, 12), 221 (45), 179 (32), 155 (26), 123 (26), 121 (30), 109 (30), 97 (71), 81 (26), 69 (91), 57 (100), 55 (42), 43 (32), and 41 (84).

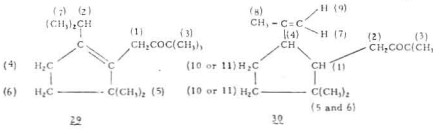
22

Anal. Calcd for $C_{16}H_{24}O$: C, 81.29; H, 11.94. Found: C, 81.52; H, 12.10.

When the reaction time or the amount of TsOH catalyst used in this dehydration procedure was increased, the crude product contained (glpc, silicone SE-30 on Chromosorb P) various mixtures of the cyclized products 25 (ret. time 18.0 min), 24 (23.4 min), and 23 (21.8 min) as well as the enone 22d (28.0 min) and a component thought to be enone 28 (26.2 min). When a PhH solution of 6.1 mmol of the aldol 21d and 0.2 mmol of TsOH was refluxed for 60 min before product isolation, the product yields were estimated (glpc and nmr analysis) to be 59% of 25, 5% of 24, and 3% of 23. From a comparable reaction employing a reflux period of only 10 min, the estimated yields were 1% of 25, 8% of 24, 60% of 23, 3% of 22d and 4% of 28.

A collected (glpc) sample of the ketone 25 was obtained as white needles, mp 31°; ir (CCl_4), 1710 cm^{-1} (C=O); uv (95% EtOH), end absorption with ε 2700 at 210 mμ; mass spectrum, m/e (rel. intensity), 236 (M^+, 3), 95 (16), 57 (100), 43 (25), and 41 (19); nmr (CCl_4), δ 3.10 (2H, broad, CH_2CO), 2.0-2.5 (3H, m, CH and allylic CH_2), 1.3-1.8 (2H, m, CH_2), 1.16 (9H, s, t-Bu), 0.95 (6H, d, J = 7 Hz, CH_3), and 0.86 (6H, s, CH_3). When a CCl_4 solution of the ketone 25 was treated with successive increments of the nmr shift reagent Eu (dpm)$_3$, the relative shifts, Δδ, for the various protons followed the order indicated in the structure 29 (where No. 1 represents the largest shift and No. 7 the smallest).

Anal. Calcd for $C_{16}H_{24}O$: C, 81.29; H, 11.94. Found: C, 81.33; H, 11.97.



29 30

23

A collected (glpc) sample of the minor cyclized product 24 was obtained as a liquid: ir (CCl_4), 1705 cm^{-1} (C=O); nmr (CCl_4), δ 1.8-3.1 (5H, m, allylic CH and CH_2 and CH_2CO), 1.58 (6H, broad, s, allylic CH_3), 1.1-1.5 (2H, m, CH_2), 1.07 (9H, s, t-Bu), 0.92 (3H, s, CH_3), and 0.83 (3H, s, CH_3); mass spectrum, m/e (rel. intensity), 236 (M^+, 5), 221 (5), 137 (18), 121 (18), 95 (20), 85 (15), 57 (100), and 41 (20).

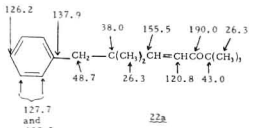
Anal. Calcd for $C_{16}H_{24}O$: C, 81.29; H, 11.94. Found: C, 81.29; H, 11.97.

A collected (glpc) sample of ketone 23 was obtained as a liquid that solidified at 15°; ir (CCl_4), 1705 (C=O), 1640 (C=C), and 900 cm^{-1} (C=CH_2); mass spectrum, m/e (rel. intensity), 236 (M^+, 3), 221 (10), 136 (27), 121 (89), 109 (26), 95 (70), 91 (25), 87 (24), 57 (100), and 41 (41); nmr (CCl_4), δ 4.6-4.7 (2H, m, vinyl CH), 2.1-2.4 (3H, m, allylic CH and CH_2CO), 1.3-1.8 (7H, m, CH_2 and allylic CH_3), 1.10 (9H, s, t-Bu), 0.98 (3H, s, CH_3), and 0.82 (3H, s, CH_3). When a CCl_4 solution of the ketone 23 was treated with successive increments of the nmr shift reagent, Eu(fod)$_3$, the relative shifts, Δδ, for the various protons followed the order indicated in structure 30 (where No. 1 is the largest shift).

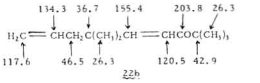
Anal. Calcd for $C_{16}H_{24}O$: C, 81.29; H, 11.94. Found: C, 81.48; H, 12.09.

^{13}C NMR Spectra of the Enones 22. -- The natural abundance ^{13}C nmr spectrum of each of these enones was measured in $CDCl_3$ solution with added TMS as an internal standard. In each case the spectrum was measured both with broadband proton decoupling and with off-resonance decoupling. The chemical shift assignments, indicated in ppm in the accompanying structures, are compatible both with the off-resonance decoupling experiments and with expected chemical shift values for carbon atoms in similar environments.[11]

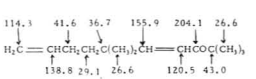
24



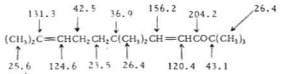
22a



22b



22c



22d

be preferred over the original procedure (refluxing aqueous 10% mineral acid)[6] since the hydrolysis is *faster* and acid-catalyzed side reactions (*e.g.*, double-bond isomerization) are largely avoided. By attention to the foregoing details, each of the desired aldehydes **16** was synthesized in good yield and contamination of aldehydes **16c** and **16d** with their double-bond isomers **18b** and **19b** was minimized.

With the aldehydes **16** in hand, application of a previously described[9] aldol condensation procedure in which each aldehyde **16** was added to a *cold* (−40 to −50°) *ether solution* of the lithium enolate **20** (Scheme II) produced the aldol products **21** in high yield. Subsequent dehydration of the aldols **21** with a catalytic amount of TsOH in PhH afforded the indicated trans enones **22,** three of which could be isolated as low-melting crystalline materials.

Although the conditions used for the acid-catalyzed dehydration of the aldols **21a, 21b,** and **21c** to the corresponding enones **22** were not particularly critical (*ca* 0.1 molar equiv of TsOH in boiling PhH), the enone **22d** proved to be especially prone to subsequent acid-catalyzed cyclization. Thus, attempts to dehydrate the aldol **21d** with 0.1 molar equiv of TsOH in boiling PhH formed primarily the cyclic keto olefins **23–25,** presumably by successive conversion of the enone **22d** to the carbonium ion intermediates **26** and **27.** With much less acid catalyst (*ca* 0.001 molar equiv) and a short reaction time, the dehydration reaction could be stopped at the desired stage to form the enone **22d.** The ease of this acid-catalyzed cyclization **22a** → **23–25** is, of course, gratifying support for our expectation that cyclization of electron-deficient intermediates derived from the enone **22d** will be a favorable process.

Registry No.—**3,** 78-84-2; **4,** 14498-14-9; **5,** 6283-77-8; **6,** 32970-42-6; **7,** 6852-60-4; **8a,** 52278-93-0; **9,** 627-27-0; **10,** 5162-44-7; **11,** 1462-10-8; **12,** 52278-94-1; **13,** 930-39-2; **14a,** 2270-59-9; **15a,** 52278-95-2; **15b,** 52278-96-3; **15c,** 52278-97-4; **15d,** 52278-98-5; **16a,** 1009-62-7; **16b,** 5497-67-6; **16c,** 52278-99-6; **16d,** 52279-00-2; **16e,** 996-12-3; **17,** 13351-61-6; **18b,** 52341-50-1; **21a,** 52279-01-3; **21b,** 52279-02-4; **21c,** 52279-03-5; **21d,** 52279-04-6; **22a,** 52279-05-7; **22b,** 52279-06-8; **22c,** 52279-07-9; **22d,** 52279-08-0; **23,** 52279-09-1; **24,** 52279-01-4; **25,** 52279-11-5; **28,** 52279-12-6; allyl bromide, 106-95-6; methyl cyclopropyl ketone, 765-43-5.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprint-

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References and Notes

(1) This research has been supported by Public Health Service Grant 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) (a) K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, and D. K. Roe, *J. Amer. Chem. Soc.*, **92**, 2783 (1970); (b) H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *ibid.*, **92**, 2800 (1970).
(3) H. K. Dietl and K. C. Brannock, *Tetrahedron Lett.*, 1273 (1973).
(4) For applications of these two procedures in the preparation of specific enolate anions from ketones, see H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971), and references cited therein.
(5) (a) T. A. Geissman, *Org. React.*, **2**, 94 (1944); (b) C. A. Buehler and D. E. Pearson, "Survey of Organic Syntheses," Wiley-Interscience, New York, N.Y., 1970, pp 199, 853–855.
(6) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).
(7) (a) G. Wittig and A. Hesse, *Org. Syn.*, **50**, 66 (1970); (b) D. A. Evans, *J. Amer. Chem. Soc.*, **92**, 7593 (1970); (c) G. Stork and J. Benaim, *ibid.*, **93**, 5938 (1971); (d) A. I. Meyers, *et al.*, *J. Org. Chem.*, **38**, 36 (1973); (e) T. Cuvigny, H. Normant, and P. Hullot, *Bull. Soc. Chim. Fr.*, 3876 (1970).
(8) (a) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **85**, 2843 (1963); (b) J. Hine, J. C. Craig, Jr., J. G. Underwood, and F. A. Via, *ibid.*, **92**, 5194 (1970).
(9) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Amer. Chem. Soc.*, **95**, 3310 (1973).
(10) 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 237 or Model 257 infrared recording spectrophotometer fitter with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The proton nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrometer and the ^{13}C nmr spectra were obtained at 100 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shifts are expressed in δ values (parts per million) 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.
(11) This experiment was performed in our laboratories by Mr. Larry E. Huber.
(12) P. Z. Bedoukian, *J. Amer. Chem. Soc.*, **66**, 1325 (1944).
(13) H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **90**, 2915 (1968).
(14) For examples, see M. Gall and H. O. House, *Org. Syn.*, **52**, 39 (1972), and ref 4.
(15) R. Wegscheider and E. Spath, *Monatsh. Chem.*, **30**, 825 (1909).
(16) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957).
(17) This procedure was developed by R. I. Trust and R. E. Ireland, *Org. Syn.*, **53**, 116 (1973).
(18) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951).
(19) N. S. Johary and L. N. Owen, *J. Chem. Soc.*, 1292 (1955).
(20) M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. Fr.*, 1072 (1960).
(21) W. H. Urry, F. W. Stacey, E. S. Huyser, and O. O. Juveland, *J. Amer. Chem. Soc.*, **76**, 450 (1954).
(22) The procedure has been described by L. Willimann and H. Schinz, *Helv. Chim. Acta*, **35**, 2401 (1952).
(23) For a detailed description of this procedure, see ref 4 and 14.
(24) The relatively rapid cleavage of DME by strong bases (RLi, i-Pr_2NLi) at temperatures above 0–10° has been noted previously. See ref 4 and H. Gilman, A. H. Haubein, and H. Hartzfeld, *J. Org. Chem.*, **19**, 1034 (1954).
(25) The optimum rate of imine hydrolysis is expected at *ca.* pH 4; see ref 8.
(26) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961).
(27) P. Warrick, Jr., and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **84**, 4095 (1962).
(28) (a) G. Opitz, H. Hellmann, H. Mildenberger, and H. Suhr, *Justus Liebigs Ann. Chem.*, **649**, 36 (1961); (b) G. Opitz, H. Hellmann, and H. W. Schubert, *ibid.*, **623**, 112 (1959).
(29) K. C. Brannock, *J. Amer. Chem. Soc.*, **81**, 3379 (1959).
(30) L. A. Shutikoya, K. V. Puzitskii, V. G. Cherkaev, and Ya. T. Eidus, *Tr. Vses. Nauch.-Issled. Inst. Sin. Natur. Dushistykh Veshchestv*, **No. 7**, 16 (1965); *Chem. Abstr.*, **66**, 85413 (1966).
(31) (a) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N.Y., 1972; (b) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N.Y., 1972.

Reduction of Phenyl Trifluoromethyl Ketone with Halomagnesium Alkoxides. An Almost Irreversible Meerwein–Ponndorf–Verley-Type System

James D. Morrison* and Robert W. Ridgway

Department of Chemistry, Parsons Hall, University of New Hampshire, Durham, New Hampshire 03824

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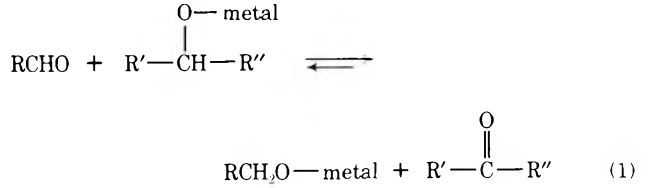
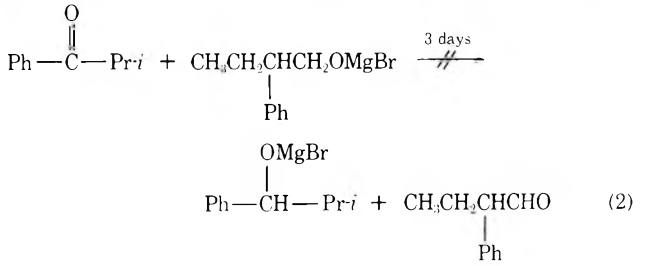
Phenyl trifluoromethyl ketone is reduced rapidly by both primary and secondary bromomagnesium alkoxides to phenyltrifluoromethylcarbinol (as the bromomagnesium salt). Using deuterium-labled alkoxides and chiral alkoxides it was shown that whereas Meerwein–Ponndorf–Verley-type reduction of phenyl trifluoromethyl ketone is facile, the alkoxide produced has little tendency to transfer its hydride to acceptor carbonyl compounds present in the reaction mixture. The electron-withdrawing inductive effect of the trifluoromethyl group is believed to be responsible for this behavior.

Meerwein–Ponndorf–Verley-type reductions (MPV reductions) are equilibrium reactions[1,2] which show a strong preference for the formation of primary alcoholate and ketone in equilibria involving primary and secondary alcoholates[3] (eq 1). A few examples of reductions of ketones by

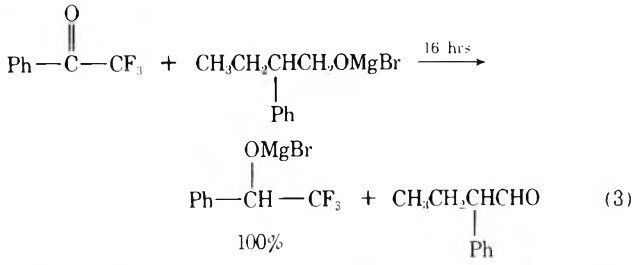


primary alcoholates have been reported[4] but in these cases the reaction was forced to completion by distillation of the aldehyde as it was formed.

In agreement with the above view of the MPV-type reaction we found that treatment of isopropyl phenyl ketone with 2-phenyl-1-butoxymagnesium bromide in ether–benzene at room temperature for 3 days gave no detectable (glpc) amount of isopropylphenylcarbinol after hydrolysis (eq 2). In contrast, we found that phenyl trifluoromethyl



ketone was essentially completely reduced in 16 hr by 2-phenylbutoxymagnesium bromide in ether–benzene at room temperature (eq 3). A similar reaction between 2-



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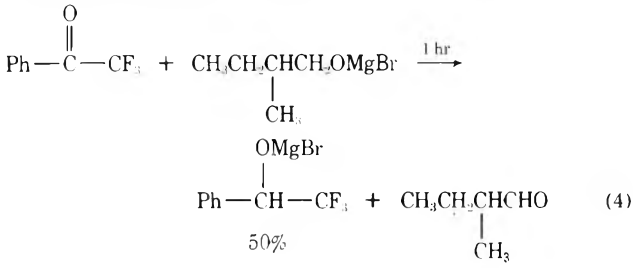
methyl-1-butoxymagnesium bromide and phenyl trifluoromethyl ketone was 50% complete in only 1 hr (eq 4). Also



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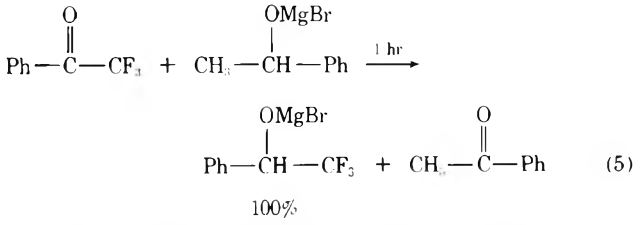
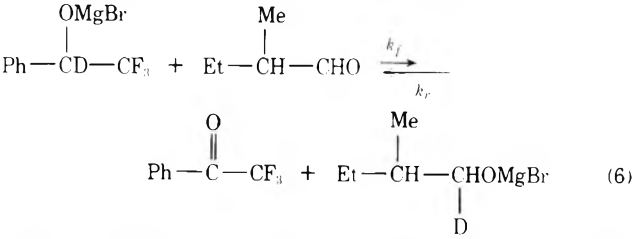
striking was the observation that the bromomagnesium salt of methylphenylcarbinol completely reduced phenyl trifluoromethyl ketone in only 1 hr under the same conditions (eq 5).



(5)

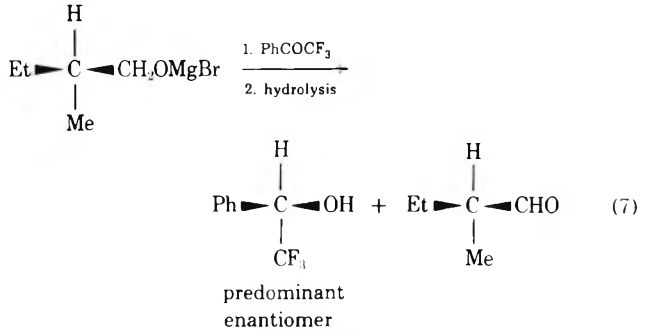
A more esoteric test of the reversibility of the magnesium alkoxide reduction of phenyl trifluoromethyl ketone was also carried out. The bromomagnesium salt of phenyltrifluoromethylcarbinol labeled with deuterium at the carbinol carbon was allowed to stand in ether–benzene solution with 2-methylbutanal for 36 hr (eq 6). The solution was then hy-



(6)

drolyzed and the phenyltrifluoromethylcarbinol isolated was found to contain 95% of the original deuterium. In addition to the driving force toward primary alcoholate the 2-methylbutanal substrate provides a partial "trap" for any deuterium that is transferred from the phenyltrifluoromethylcarbinol salt by virtue of the isotope effect which would favor the loss of hydrogen rather than deuterium from the primary alcoholate in the reverse reaction. Therefore, the very small loss of deuterium implies that there is little tendency for the phenyltrifluorocarbinol salt to transfer its carbinol hydrogen to an aldehyde. Yet, as eq 4 indicates, unlabeled 2-methylbutoxymagnesium bromide reduces phenyl trifluoromethyl ketone rapidly. Thus it is clear that $k_r \gg k_f$; the reduction of phenyl trifluoromethyl ketone by primary or secondary bromomagnesium alkoxides is negligibly reversible at room temperature in ether–benzene solvent for reaction times sufficient to allow appreciable reduction of the ketone. In other words, for all practical purposes such reductions come close to being kinetically controlled.

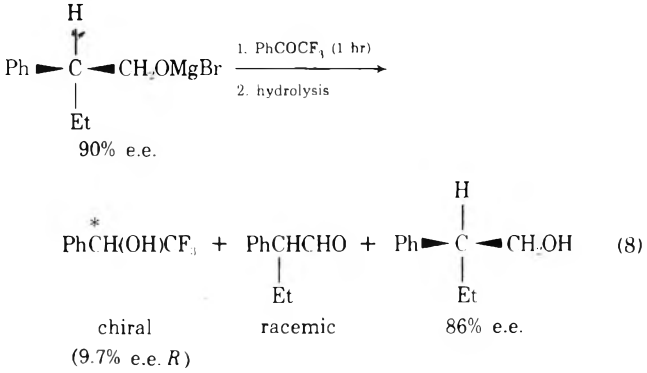
Additional evidence was provided by experiments with salts of optically active alcohols as reducing agents. For example, when phenyl trifluoromethyl ketone was reduced with (*S*)-2-methyl-1-butoxymagnesium bromide (98% optical purity) the phenyltrifluoromethylcarbinol obtained on hydrolysis was enriched in the *R* enantiomer to the extent of 4.9% for a reaction time of 1 hr (eq 7). When the same re-



(7)

duction was allowed to proceed for 26 hr a 5.3% e.e. of the *R* enantiomer was obtained.[5] In other words, there was, within experimental error, no change in per cent enantiomeric excess with an extended reaction time. This is in contrast to most asymmetric MPV-type reductions, which tend toward racemized product as the reaction time is lengthened owing to the equilibrium nature of the reaction (thermodynamic control).[6]

Furthermore, in a study of the reaction of (*S*)-2-phenyl-1-butoxymagnesium bromide (90% e.e.) with phenyltrifluoromethyl ketone (eq 8), it was found that the aldehyde by-



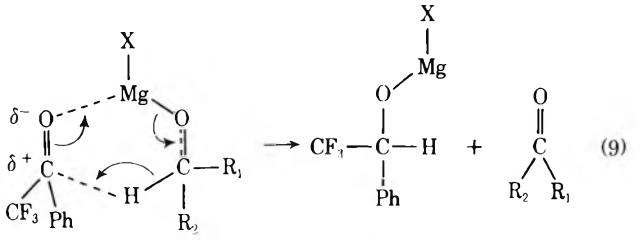
(8)

product, chiral 2-phenylbutanal, racemized under the reaction conditions. However, in an incomplete reaction (ether–benzene solvent, 1 hr reaction time) unreacted alcoholate was hydrolyzed to 86% e.e. (*S*)-2-phenyl-1-butanol. The racemized aldehyde by-product could, in principle, revert to racemic 2-phenyl-1-butoxymagnesium bromide by a MPV-type reaction with the bromomagnesium salt of phenyltrifluoromethylcarbinol or by the same type of reaction with unreacted, chiral 2-phenyl-1-butoxymagnesium bromide. Apparently under the reaction conditions used it undergoes neither of these reactions to a significant extent. Substantial equilibration by either pathway would be reflected in a significantly lower per cent enantiomeric excess for the recovered 2-phenyl-1-butanol from hydrolysis of the 2-phenyl-1-butoxymagnesium bromide. In fact, the enantiomeric purity of recovered 2-phenyl-1-butanol was only 4% lower than that of the starting material.

The results described in this paper are explicable in terms of the mechanism of MPV-type equilibrations and the electronic influence of the trifluoromethyl group. Dis-

parate chemical behavior for carbonyl groups adjacent to perfluoroalkyl groups is a recognized phenomenon.[7]

Compared to the reduction of sterically similar phenyl alkyl ketones the reduction of phenyl trifluoromethyl ketone with a halomagnesium alkoxide should take place more readily, because the strongly electron-withdrawing trifluoromethyl group will make the carbonyl carbon relatively more positive. This will facilitate a hydride-like transfer from the halomagnesium alkoxide, possibly *via* a reduction mode like that represented in eq 9.[8] In order for



(9)

the reverse reaction to occur the halomagnesium salt of phenyltrifluoromethylcarbinol would have to undergo loss of "hydride" from the carbinol carbon. It seems reasonable to expect this process to be impeded by the inductive influence of the trifluoromethyl group. Thus the inductive effect rationalizes both the fact that phenyl trifluoromethyl ketone is rapidly reduced and the fact that once hydrogen is transferred to this ketone it "sticks." Because the MPV-type reduction of phenyl trifluoromethyl ketone is so facile and is an "almost irreversible" reaction a quantitative stereochemical comparison of a wide variety of chiral halomagnesium alkoxide reducing agents under "kinetically controlled" conditions is made feasible. With other ketones meaningful comparisons of the stereochemical results of asymmetric MPV-type reductions with different reducing agents, as well as examples of high asymmetric reduction, are not readily attainable. In many cases the ketone is not readily reduced or partial racemization makes quantitative stereochemical comparisons unwarranted, or both factors conspire to prevent such investigations. We intend to elaborate the stereochemical details of asymmetric MPV-type reductions of phenyl trifluoromethyl ketone in future publications.

The asymmetric reductions reported in this paper (eq 7 and 8) involve competitive transfer of diastereotopic hydrogens from chiral alkoxides to enantiotopic faces of the ketone. In terms of the symmetry arguments that apply to such systems these reductions are similar to certain asymmetric Grignard reductions that have been described previously.[9,10]

Experimental Section

2,2,2-Trifluoro-1-phenylethanol-*1-d*. The deuterium-labeled alcohol was prepared by hydrogenation of trifluoromethyl phenyl ketone (10.4 g, 0.060 mol) with deuterium using ethyl acetate (150 ml) as solvent and predeuterated 5% palladium on carbon as catalyst. Deuterium uptake stopped short of the theoretical amount, but no attempt was made to complete the reaction because the ketone and carbinol are readily separated by distillation. The carbinol was isolated as a clear liquid, bp 73–75° (10 mm) (6.0 g, 58% yield), shown by integration of its nmr spectrum to contain 21% hydrogen at the carbinol position (average of 30 integrations).

(+)-(*S*)-2-Phenylbutanoic Acid. 2-Phenylbutanoic acid was resolved following the procedure of Levine and coworkers.[11] Racemic acid (100 g, 0.61 mol) provided, after four recrystallizations of the cinchonidine salt from 70% ethanol–water, hydrolysis, and distillation, (+)-(*S*)-2-phenylbutanoic acid (60.5 g, 0.37 mol) as a clear liquid: bp 120–122° (1.0 mm); $[\alpha]^{27}D$ +83.9°)neat); 88% e.e. based on a maximum rotation of $[\alpha]^{23}D$ +95.8° (neat).[12]

The mother liquors from several cinchonidine resolutions were combined, evaporated, and hydrolyzed to furnish (−)-(*R*)-2-phenylbutanoic acid: bp 117–118° (0.4 mm); $[\alpha]^{25}D$ −58.4° (neat); 61% e.e.

(+)-(*S*)-2-Phenyl-1-butanol. The *S* alcohol was prepared by the reduction of (+)-(*S*)-2-phenylbutanoic acid, $[\alpha]^{27}D$ +83.9° (neat), 88% e.e. (25.0 g, 0.152 mol), with $LiAlH_4$ (7.0 g, 0.18 mol) in ether (150 ml). After acid hydrolysis, the alcohol (18.4 g, 81%) was isolated as a clear liquid: bp 63–69° (0.4 mm); $[\alpha]^{25}D$ +14.9° (neat); 90% e.e., based on a maximum rotation of $[\alpha]^{25}D$ +16.5° (neat).[13]

Meerwein–Ponndorf–Verley Reductions. A round-bottomed, three-necked flask fitted with a magnetic stirrer, pressure-equalizing addition funnel, reflux-distillation head, septum cap, and nitrogen inlet was flamed dry under a stream of nitrogen. An aliquot of a filtered and standardized solution of *n*-propylmagnesium bromide in ether was injected with a nitrogen-flushed syringe. The alcohol precursor of the magnesium alkoxide was added in benzene *and the solvent composition was adjusted by distillation to a constant boiling point of 55–56°*. The ketone to be reduced was then added in one portion in a small amount of dry benzene to provide clear, homogeneous solutions about 1 *M* in alcoholate. The mixture was stirred at ambient temperatures for the stated reaction time, before being hydrolyzed with ammonium chloride solution. The organic layer was separated, combined with two or three ether extracts of the aqueous layer, dried ($MgSO_4$), and concentrated. Trifluoromethyl phenyl ketone and trifluoromethylphenylcarbinol give very characteristic infrared absorptions at 960 and 1270 cm^{-1}, respectively, which allowed a semiquantitative analysis of the extent of reduction to be carried out on the crude products. The carbinol and ketone were partially separated by distillation and the trifluoromethylphenylcarbinol was purified by preparative glpc on Carbowax 20M (180°) and Apiezon L (175°) columns. Rotation samples of trifluoromethylphenylcarbinol were analyzed by glpc and ir and shown to contain less than 1% of achiral by-products and much less than 1% of any chiral impurities. The ir spectra of purified products were all identical with that of a carefully purified sample of phenyltrifluoromethylcarbinol, and were especially revealing in the region of 2800–3000 cm^{-1} (aliphatic C–H stretch). Most impurities absorb strongly in this region but phenyltrifluoromethylcarbinol gives only a weak absorption.

Reduction of 2-Methylbutanal with 2,2,2-Trifluoro-1-phenylethoxymagnesium Bromide-*1-d* in Ether-Benzene. The alcoholate was prepared from 2,2,2-trifluoro-1-phenylethanol-*1-d* (5.00 g, 0.0284 mol) containing 21% hydrogen at the carbinol position, by reaction with ethereal *n*-propylmagnesium bromide (18 ml, 1.7 *N*, 0.030 mol) in dry benzene. The solvent composition was adjusted by distillation to 55–56°, 2-methy-1-butanal (4.90 g, 0.057 mol) in a small amount of dry benzene was added, and the mixture was stirred for 36 hr. The ir spectrum of the crude product mixture showed that both trifluoromethylphenylcarbinol and 2-methylbutanol were present. The work-up gave 4.3 g of liquid, bp 70–76° (10 mm), which on preparative glpc furnished a sample of trifluoromethylphenylcarbinol shown by integration of its nmr spectrum to contain 25% hydrogen at the carbinol position (average of 30 integrations).

Reduction of Phenyl Trifluoromethyl Ketone. With (*S*)-2-Methyl-1-butoxymagnesium Bromide in Ether–Benzene, 1 Hr. The alcoholate was prepared from an ether solution of *n*-propylmagnesium bromide (30 ml, 1.6 *N*, 0.048 mol) and (−)-(*S*)-2-methyl-1-butanol, $\alpha^{26}D$ −4.70° (neat), 98% e.e. (4.40 g, 0.050 mol), in dry benzene. Solvent composition was adjusted by distillation to 55–56°. Trifluoromethyl phenyl ketone (8.5 g, 0.048 mol) dissolved in a small amount of dry benzene was added, and the mixture was stirred for 1 hr. The ir spectrum of the crude product mixture indicated that about 50% reduction had occurred. After work-up, distillation gave three fractions: 0.5 g, bp 122–130° (1 atm); 2.8 g, bp 30–70° (10 mm); and 3.6 g, bp 73–95° (10 mm). Preparative glpc of fraction 3 gave trifluoromethylphenylcarbinol: $\alpha^{21}D$ −2.03° (neat, l = 1) [lit.[14] $\alpha^{26}D_{max}$ −41.18° (neat, l = 1), $[\alpha]^{26}D$ −31.85°]; 4.9% e.e.

With (*S*)-2-Methyl-1-butoxymagnesium Bromide in Ether–Benzene, 26 Hr. The alcoholate was prepared from an ether solution of *n*-propylmagnesium bromide (28 ml, 1.7 *N*, 0.048 mol) and (−)-(*S*)-2-methyl-1-butanol, $\alpha^{26}D$ −4.70° (neat), 98% e.e. (4.40 g, 0.050 mol), in dry benzene. Solvent composition was adjusted by distillation to 55–56°. Trifluoromethyl phenyl ketone (7.80 g, 0.045 mol) was added in a small amount of dry benzene and the mixture was stirred for 26 hr. Distillation of the products gave 5.4 g of material, bp 73–75° (10 mm), $\alpha^{21}D$ − 2.04° (neat), which on preparative glpc furnished phenyltrifluoromethylcarbinol, $\alpha^{19}D$ −2.20° (neat, l = 1), 5.3% e.e.[14]

With (*S*)-2-Phenyl-1-butoxymagnesium Bromide in Ether–Benzene. 1 Hr. The alcoholate was prepared from an ether solution of *n*-propylmagnesium bromide (31 ml, 1.6 *N*, 0.050 mol), (+)-(*S*)-2-phenyl-1-butanol, $\alpha^{25}D$ +14.9° (neat), 90% e.e. (8.25 g, 0.055 mol), in dry benzene. Solvent composition was adjusted by distillation to 55–56°. Trifluoromethyl phenyl ketone (8.50 g, 0.048 mol) dissolved in a small amount of dry benzene was added to provide a clear solution which formed a precipitate while the reaction mixture was stirred for 1 hr. Work-up gave four fractions: 2.3 g, bp 32–79° (10 mm); 3.2 g, bp 70–90° (10 mm); 1.2 g, bp 90–105° (10 mm); and 3.9 g, bp 86–90° (1 mm). Preparative glpc of the second fraction provided trifuloromethylphenylcarbinol, $\alpha^{26}D$ −4.0° (neat, l = 1), 9.7% e.e., and a sample of 2-phenylbutanal, $\alpha^{27}D$ 0.000° (neat). Preparative glpc of the fourth fraction provided (+)-(*S*)-2-phenyl-1-butanol, $[\alpha]^{27}D$ +14.25° (neat), 86% e.e.

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Registry No.—(+)-(*S*)-2-Phenylbutanoic acid, 4286-15-1; (−)-(*R*)-2-phenylbutanoic acid, 938-79-4; (+)-(*S*)-2-phenyl-1-butanol, 33442-47-6; trifluoromethyl phenyl ketone, 434-45-7; 2-methylbutanal, 96-17-3; 2,2,2-trifluoro-1-phenyl-ethanol-*1-d*, 2793-54-6; *n*-propyl bromide, 106-94-5; (−)-(*S*)-2-methyl-1-butanol, 1565-80-6; (−)-trifluoromethylphenylcarbinol, 10531-50-7.

References and Notes

(1) A. L. Wilds, *Org. React.*, **2**, 178 (1944).
(2) T. Bersin in "Newer Methods of Preparative Organic Chemistry," W. Foerst, Ed., English translation and revision by E. R. Webster and J. V. Crawford, Interscience, New York, N. Y., 1948, pp 125–153.
(3) H. Adkins, *et al.*, *J. Amer. Chem. Soc.*, **71**, 3622 (1949).
(4) S. Yamashita, *J. Organometal. Chem.*, **11**, 377 (1968).
(5) We will use the designation % e.e. (per cent enantiomeric excess) to express the degree of optical purity; *i.e.*, 5% e.e. of the *R* enantiomer means that the % *R* enantiomer − % *S* enantiomer = 5%.
(6) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, Chapter 5.
(7) H. P. Braendlin and E. T. McBee, *Advan. Fluorine Chem.*, **3**, 1 (1963).
(8) We do not know the exact timing of the electron shifts embodied in the hydrogen transfer illustration in eq 9. There could be complex formation by coordination of the carbonyl oxygen to magnesium prior to hydrogen transfer. However, the six-membered transition state model appears to be a reasonable working hypothesis.
(9) (a) J. D. Morrison, D. L. Black, and R. W. Ridgway, *Tetrahedron Lett.*, 985 (1968); (b) J. D. Morrison and R. W. Ridgway, *J. Amer. Chem. Soc.*, **91**, 4601 (1969).
(10) For related cases see (a) L. Lardicci, G. P. Giacomelli, and R. Menicagli, *Tetrahedron Lett.*, 687 (1972). (b) D. Nasipuri, C. K. Ghosh, and R. J. L. Martin, *J. Org. Chem.*, **35**, 657 (1970), and references cited therein.
(11) (a) P. A. Levine, L. A. Mikesta, and K. Passoth, *J. Biol. Chem.*, **88**, 27 (1930); (b) K. Peterson, *Ark. Kemi*, **10**, 283 (1956).
(12) A. Weidler and G. Bergson, *Acta Chem. Scand.*, **18**, 1483 (1964).
(13) J. S. Birtwhistle, *et al.*, *J. Org. Chem.*, **29**, 37 (1964).
(14) D. M. Feigl and H. S. Mosher, *J. Org. Chem.*, **33**, 4242 (1968).

Preparation and Aluminum Chloride Induced Rearrangement of Cyclopropylpyridines

John J. Eisch,* Harsh Gopal, and David A. Russo

Department of Chemistry, The State University of New York at Binghamton, Binghamton, New York 13901

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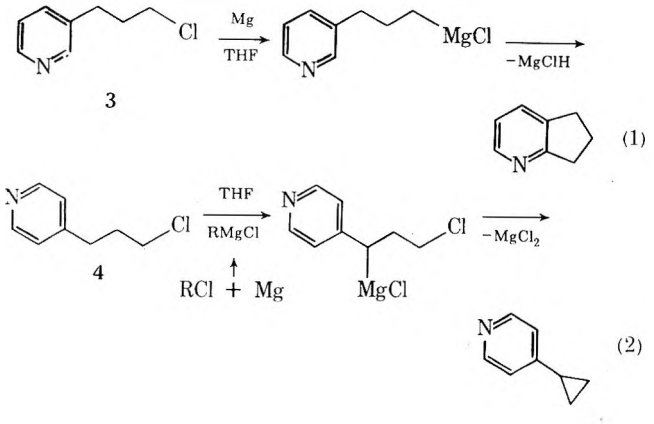
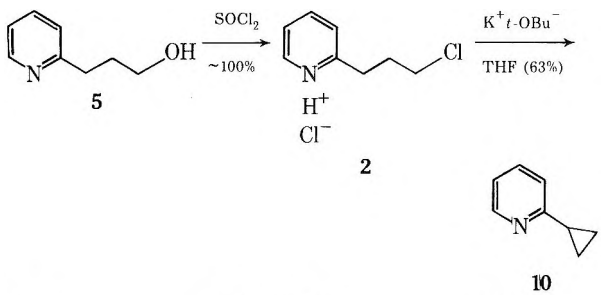
A convenient, two-step preparation of both 2- and 4-cyclopropylpyridines from the corresponding 3-(2- or 4-pyridyl)propanols consists of treatment with thionyl chloride and dehydrohalogenation of the resulting chlorides with potassium *tert*-butoxide. The analogous 3-(3-pyridyl)propanol was converted to *trans*-3-propenylpyridine by a similar procedure. Although the 2- and 4-cyclopropylpyridines were remarkably stable to strong bases, mineral acids, heat, and ultraviolet radiation, they did decompose at *ca.* 400° and were especially reactive toward anhydrous aluminum chloride at 25–45°. Thermally, the 2 isomer yielded 2-picoline, 2-*n*-propylpyridine, ethylene, acetylene, and polymeric material. In the presence of aluminum chloride, both the 2 and 4 isomers gave the corresponding *trans*-propenyl-, isopropenyl-, (2-chloropropyl)-, and (1-chloro-2-propyl)pyridines.

A recent study[1] of the carbocyclization reactions of pyridine derivatives has uncovered two novel reactions of synthetic potential: (1) the first formation of carboannulated pyridine derivatives by intramolecular nucleophilic attack[2] (eq 1); and (2) the detection of 4-cyclopropylpyridine from the reaction of 4-(3-chloropropyl)pyridine with magnesium metal (eq 2). Since the existing syntheses of cyclopropylpyridines are limited in number and in scope, the dechlorometalative closure to the cyclopropane, depicted in eq 2, seemed worth developing as a new synthetic method. Many of the known methods involve more steps or are low yielding.[3] Another approach, namely, the addition of diazoalkanes[4] or sulfonium methylides[5] to vinylpyridines, gives good yields and is convenient, if the appropriate pyridine starting material is available.



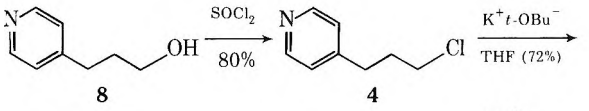
The cyclization of 2- and 4-(3-chloropropyl)pyridines by base has proved to be an advantageous route to the respective cyclopropylpyridines, because the conversion of the commercially available propanols to the chloropropanes and thence to the cyclopropanes requires only two steps and gives good overall yields. The enhanced acidity of the methylene groups α to the ring permits a facile formation of the anionic center needed for ring closure (*cf.* eq 2). With the use of 2 equiv of potassium *tert*-butoxide these reactions could be carried out on the isolated, but unpuri-

fied, hydrochloride salts (*e.g.*, **2**), thus further simplifying the procedure. In fact, for the 2-(3-chloropropyl)pyridine preparation, the use of **2** prevents altogether the ready tendency of the free pyridine base to undergo intramolecular quaternization to the known 1,2-dihydro-3*H*-pyrrocolinium salt.[6]

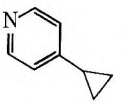


5 2

10 (3)

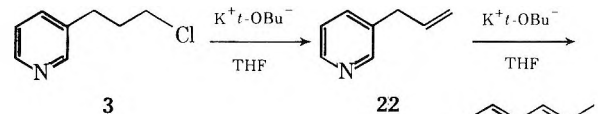


8 4

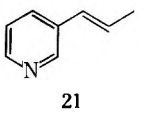


16 (4)

The foregoing method would be potentially applicable to any 2- or 4-alkylpyridines which could be transformed to the requisite propanols by base-catalyzed reaction with ethylene oxide. That the method fails with 3-(3-chloropropyl)pyridine (**3**) should not be surprising; the lowered acidity of the methylene group α to the ring means that a straightforward dehydrochlorination can compete readily. The observed product, *trans*-3-(1-propenyl)pyridine (**21**), has also been shown to form readily when pure 3-allylpyridine (**22**) is treated with this base in THF.[7]



3 22

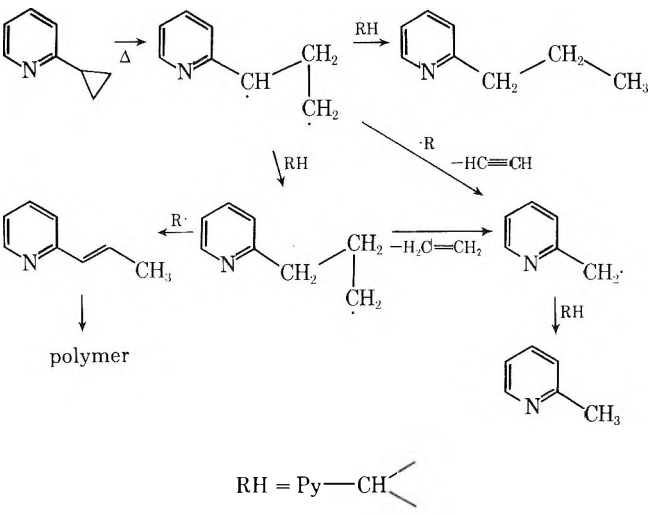


21 (5)

The ready formation of these cyclopropylpyridines raised the converse point, namely, how resistant such rings would be to rupture. As in recent work,[5] further attempts to cleave **10** or **16** by prolonged treatment with potassium *tert*-butoxide led to no nucleophilic rupture. Similarly, attempts with strong mineral acids or irradiation at 254 nm in benzene or cyclohexane solution showed the ring to be inert. Only by heating 2-cyclopropylpyridine in the vicinity of 400° could rupture be achieved, but then the decomposition was profound. In addition to a black, polymeric glass, the observed products were 2-picoline, 2-*n*-propylpyridine, ethylene, and acetylene, suggestive of a homolytic bond rupture[8] (Scheme I).

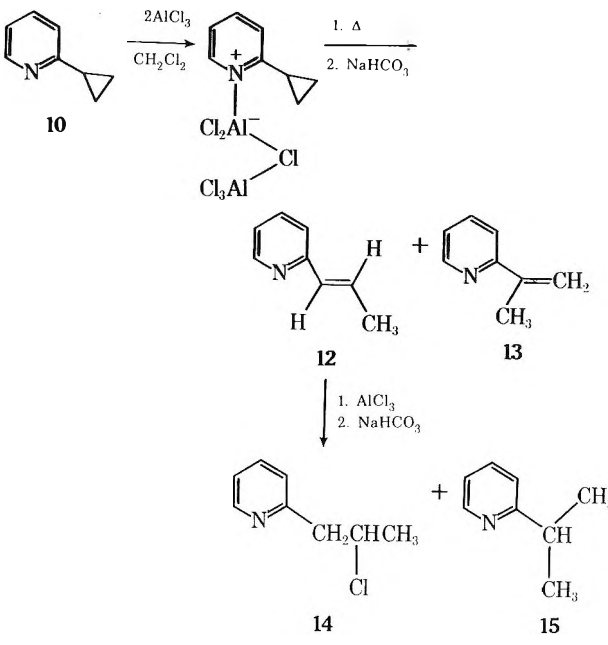
In light of the resistance of **10** and **16** to cleavage, especially by strong acids, it is therefore remarkable that both derivatives underwent rapid cyclopropyl ring opening with 2 equiv of anhydrous aluminum chloride at 25–45°. The reaction does not appear to be caused just by adventitious hydrogen chloride and catalytic amounts of $AlCl_3$, for both **10** and **16** were recovered unchanged when heated with 1 equiv of $AlCl_3$. The products obtained upon hydrolytic work-up were analogous in both cases: the corresponding *trans*-propenyl- and isopropenylpyridines, as well as the (2-chloropropyl)- and (1-chloro-2-propyl)pyridines

Scheme I



RH = Py—CH

Scheme II

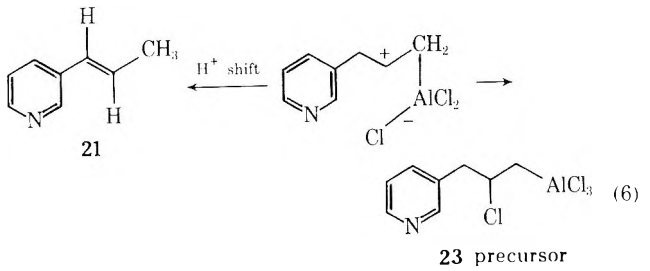


10 12 13 14 15

(Scheme II for 2-cyclopropylpyridine). When the cleavage reaction was conducted at 25°, the proportion of the chloro compounds (**14** and **15**) was higher than at 45°. This finding suggests that aluminum salts of **14** and **15** are the initially formed reaction products from **10**, but that higher temperatures cause partial dechloralumination to produce **12** and **13** (*vide supra*).

By treating pure **12** with 2 equiv of $AlCl_3$ it was shown that some **14** could be isolated. It is important to note, however, that no formation of **13** or **15** was observed from **12**. This experiment rules out the formation of the isopropylpyridines in a reaction other than the ring opening of 2-cyclopropylpyridine. Also pertinent is the behavior of a typical allylpyridine, such as the 3 isomer (**22**), toward anhydrous aluminum chloride. The observed isomerization and addition products are consistent with initial chloralumination and Lewis acid catalyzed isomerization. The conversion of **22** into **21** and **23** leaves open the possibility that, in the isomerization of cyclopropylpyridines, the 2- and 4-allylpyridines may actually be precursors to the propylpyridine derivatives, such as **12** and **14**.

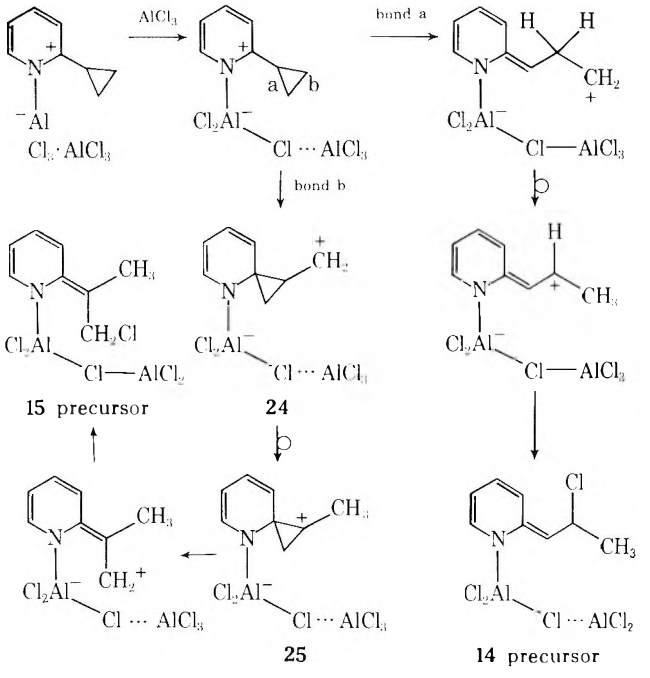
With this reservation in mind, then, the following mechanism (Scheme III) can be formulated in accordance with the experimental data: (a) the 1:1 pyridine–$AlCl_3$ complex



(6)

with a positive polarized α (with **16**, γ) position undergoes chloralumination; (b) rupture occurs principally at bond a, followed rapidly by a 1,2-hydride shift to yield the more stable carbonium ion, which is α to an enamine group;[9] (c) nucleophilic attack of chloride leads to the precursor of **14**; (d) a competing, minor, ring opening (bond b) leading to **24** could again be followed by a 1,2-hydride shift to yield a spiro cyclopropyl cation **25**, which could open up[10] to give a precursor to **15**. A precedent for such a cleavage of the cyclopropyl ring by anhydrous aluminum chloride is seen in the side-reaction cleavage of cyclopropylbenzene during an attempted Friedel–Crafts acylation.[11] In the case reported, however, hydrogen chloride may well have been a participant and, furthermore, no isopropyl products (analogous to **13** and **15**) were detected.[12]

Scheme III



Just as haloboration has begun to prove valuable in ring contraction and stereospecific hydrohalogenation reactions[13,14] so this facile chloralumination of strained carbon–carbon bonds deserves further study as a potentially useful synthetic reaction.

Experimental Section

All melting points were determined on a Thomas-Hoover, oil-bath, capillary apparatus and are uncorrected. Infrared spectra (ir) were recorded on Perkin-Elmer spectrophotometers, either Model 137 or Model 457. Proton magnetic resonance spectra (pmr) were obtained with Varian spectrometers, either Model A-60 or Model 3521A (100 MHz), on neat samples or on 10% solutions in pure solvents containing tetramethylsilane as an internal standard. Signals are reported on the δ scale in parts per million, followed by the relative proton intensities and the coupling constants (J) in hertz. Vapor phase chromatographic analysis (vpc) and isolations were carried out on an F & M chromatograph, Model 720, equipped with 12 ft × 0.25 in. dual columns of 10% silicone rubber (UC-W98) or Carbowax 20M on 60–80 mesh acid-washed firebrick. Mass spectra were recorded at Cornell University, Ithaca, N. Y., either on an AEI-MS-902 or on a Perkin-Elmer 270 spectrometer. Elemental analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

All preparations and reactions involving air- or moisture-sensitive organometallic or heterocyclic intermediates were conducted under an atmosphere of dry, oxygen-free nitrogen, with adherence to published techniques.[15] The petroleum ether had a boiling range of 30–60°; the tetrahydrofuran was made absolute just before use; and the chloroform and methylene chloride used in the aluminum chloride reactions were dried over anhydrous $CaCl_2$ and then distilled.

Fractional distillations were performed with Nester-Faust spinning-band columns, of the 6-mm (i.d.) semimicro type, of either a 6-in. or 18-in. length, equipped with a Teflon spinning band and vacuum jacketing.

General Procedure for the Preparation of the 2-, 3-, and 4-(3-Chloropropyl)pyridines. To a stirred solution of 3-(3- or 4-pyridyl)-1-propanol (**7** and **8**) or 3-(2-pyridyl)-1-propanol hydrochloride (**6**) (0.50 mol) in 250 ml of dry chloroform was added, dropwise, 1.5 equiv of thionyl chloride (90.1 g, 0.76 mol) over a 30-min period (corrosive gas evolved). The dark solution was then refluxed for 1 hr (for the 2-substituted pyridine hydrochloride, 3 hr), cooled, and finally poured onto ice. The chilled biphasic system for **7** and **8** was made basic to litmus with an ice-cooled 50% solution of aqueous KOH. (*Cf.* below for **6**.) The organic layer was separated, the aqueous layer was extracted with 500 ml of $CHCl_3$, and the combined organic fractions were dried over anhydrous Ca_2SO_4.

A. 2-(3-Chloropropyl)pyridine (1). The reaction of thionyl chloride with 3-(2-pyridyl)-1-propanol (**5**), in accordance with the foregoing procedure, does yield 2-(3-chloropropyl)pyridine (**1**), if the work-up is prompt. The nmr spectrum ($CDCl_3$) of the undistilled, but fairly pure, product was clean: δ 9.73 (d, 1, H_6-Py), 8.00–8.97 (m, H_3-, H_4-, H_5-Py), 5.16 (t, 2, $-CH_2Cl$), 3.82 (t, 2, Py–CH_2–) and 2.63 (q, 2, $-CH_2$–). Soon, however, crystalline 1,2-dihydro-3*H*-pyrrocolinium chloride (**9**)[6] began to precipitate.

For further use of the chloride, it was best prepared and isolated as its hydrochloride. Thus, gaseous HCl was first passed into a $CHCl_3$ solution of **5** and the resulting partial solution of **6** was treated with thionyl chloride.

The work-up involved the evaporative removal of the solvent under reduced pressure to leave a light brown paste of **2**, which was then washed with dry benzene. The hygroscopic powder (~100%) could be stored under nitrogen until use: nmr ($CDCl_3$) of the Py–$CH_2CH_2CH_2Cl$, δ 3.65 (t), 2.65 (q), and 3.85 (t), respectively, for the hydrochloride salt.

B. 3-(3-Chloropropyl)pyridine (3). A 74% yield of this compound was obtained: bp 60–61° (0.4 mm); $n^{24.6}$D 1.5243; ir (neat) 1580 (m), 1420 (s), 1310 (m), 1290 (m), 1030 (s), 975 (m), 795 (s), and 718 cm^{-1} (s); nmr (neat) for Py–$CH_2CH_2CH_2Cl$, δ 2.77 (t), 2.00 (m), and 3.58, respectively; picrate mp 126–128° (platelets, EtOH).

Anal. Calcd for $C_8H_{10}ClN$: C, 61.74; H, 6.48. Found: C, 61.83; H, 6.44.

C. 4-(3-Chloropropyl)pyridine (4). An 80% yield was obtained: bp 64–66° (0.4 mm); $n^{23.2}$D 1.5250; ir (neat) 1600 (s), 1410 (s), 1300 (m), 1220 (m), 1065 (m), 990 (s), 875 (m), 833 (s), 795 (s), 758 (s), and 722 cm^{-1} (m).[16]

Reactions of the x-(3-Chloropropyl)pyridines with Potassium *tert*-Butoxide. To a solution of potassium *tert*-butoxide (5.88 g, 0.052 mol) in 100 ml of absolute tetrahydrofuran, which was chilled in an ice bath, was added a solution of 3- or 4-(3-chloropropyl)pyridine (7.78 g, 0.050 mol) in 50 ml of the solvent over a 20-min period. (In the case of the 2-substituted derivative, a slurry of **2** in THF was introduced and 2.5 equiv of potassium *tert*-butoxide was used.) The resulting mixtures were stirred at 25° under a nitrogen atmosphere for 24–36 hr. The reaction mixture was treated with 200 ml of water and extracted repeatedly with $CHCl_3$. The combined extracts were dried over anhydrous $MgSO_4$ and the solvent was carefully evaporated at 40° under reduced pressure.

A. 2-Cyclopropylpyridine (10).[17] Distillation of the product from **2** (bp 57–58°, 4.5 mm) yielded 7.3 g (63%) of colorless product: ir (neat) 3003 (s), 1599 (s), 1478 (s), 1454 (s), 1434 (s), 1214 (s), 1148 (s), 1102 (s), 1022 (s), 990 (s), 903 (s), 818 (s), 774 (s), and 747 cm^{-1} (s); nmr (neat) δ 8.43 (m, H_6-Py), 7.40 (m, H_4-Py), 6.93 (m, H_3- and H_5-Py), 1.95 (m, –CH of C_3H_5), and 1.00 (m, C_2H_4 of C_3H_5); picrate mp 130–132° (needles, EtOH).

The methiodide (**11**) was a colorless solid: mp 120–121° (EtOH); nmr (CF_3CO_2H) δ 8.73 (br d, H_6-Py), 8.37 (br d, H_4-Py), 7.42 (br t,

H_3- and H_5-Py), 4.55 (s, CH_3), 2.03–2.57 (m, CH of C_3H_5), and 1.73–1.90 (m, C_2H_4 of C_3H_5).

Anal. Calcd for $C_9H_{12}IN$: C, 41.39; H, 4.63; N, 5.36. Found: C, 41.37; H, 4.53; N, 5.32.

B. 3-(*trans*-1-Propenyl)pyridine (21). By dehalogenation of **3**, **21** was the only product detected by nmr and vpc analyses, as the mixture was monitored at 1, 2, 5, 8, 18, and 24 hr of reaction. Distillative work-up provided a 75% yield: bp 70–72° (5.8 mm); ir (neat) 3005 (s), 1570 (s), 1475 (s), 1395 (s), 1115 (m), 1028 (s), 965 (s), 825 (m), 774 (s), and 703 cm^{-1} (s); nmr (neat) δ 6.26 (m, CH=CH) and 1.74 (m, 3, CH_3); picrate mp 156–157° (needles, EtOH).

C. 4-Cyclopropylpyridine (16). This product was isolated from **4** in 72% yield: bp 61–62° (3.9 mm); ir (neat) 3012 (m), 1605 (s), 1492 (m), 1457 (m), 1407 (s), 1215 (m), 1048 (m), 1025 (m), 995 (s), 906 (s), and 810 cm^{-1} (s); nmr ($CDCl_3$) δ 8.78 (m, H_2- and H_6-Py), 1.85 (m, CH of C_3H_5), and 0.92 (m, C_2H_4 of C_3H_5); picrate mp 158–160° (needles, EtOH).[3]

Reactions of 2- and 4-Chloropropylpyridines with Anhydrous Aluminum Chloride. When either of the cyclopropylpyridines (465 mg, 3.9 mmol) was heated at reflux for 12 hr with 1 equiv of anhydrous aluminum chloride (freshly sublimed, 520 mg, 3.9 mmol) in 20 ml of pure methylene chloride, usual hydrolytic work-up yielded the unchanged cyclopropylpyridine (nmr and vpc analyses) in >90% recovery.

On the other hand, when each of the cyclopropylpyridines (3.64 g, 30.6 mmol) was treated with 2 equiv of anhydrous aluminum chloride (8.15 g, 61.1 mmol) a vigorous reaction took place. After a 12-hr reflux period the solution was poured into aqueous $NaHCO_3$ solution and the resulting suspension was filtered. The separated aqueous layer was extracted with three 25-ml portions of CH_2Cl_2, the organic fractions were combined and dried over anhydrous $MgSO_4$, and the solvent was removed on a rotary evaporator. The product residue amounted to 3.3–3.4 g and was shown by vpc analysis to contain ~5% of the cyclopropylpyridine and four new components.

A. 2-Cyclopropylpyridine. By a combination of nmr and vpc analyses this mixture was shown to consist of 77% *trans*-2-propenylpyridine (**12**), 9% 2-isopropenylpyridine (**13**), 6% 2-(2-chloropropyl)pyridine (**14**), 2% 2-(1-chloro-2-propyl)pyridine (**15**), and 5% **10**.

In another run conducted for 12 hr at 25° there was 20% of remaining **10** and the ratio of **12:13:14:15** was now 4:~0:2:1. Thus, the proportion of chloro derivatives isolated was higher than at 45°.

The products were separated by chromatography on a silica gel column (2.8 × 98 cm) prepared with petroleum ether. The eluting solvent was varied from petroleum ether through mixtures with benzene and finally CH_2Cl_2, as 470 25-ml fractions were collected automatically (Instrumentation Specialties Co.). The sequence of elution was **13**, **15**, **12**, and **14**. Identification follows from these data.

***trans*-2-Propenylpyridine (12):** bp 194–195°; ir (neat) 1585 (s), 1562 (m), 1472 (s), 1443 (m), 1438 (m), 972 (s), and 772 cm^{-1} (s); nmr (neat) δ 8.57 (m of d, H_6-Py), 7.30–7.65 (m, H_4-Py), 6.37–7.26 (m, H_3- and H_5-Py, CH=CH), and 1.80 (d, CH_3, J = 5.8 Hz).

2-Isopropenylpyridine (13): nmr (neat) δ 8.62 (m of d, H_6-Py), 6.96–7.80 (m, H_3-, H_4-, and H_5-Py), 5.88 (m, Py–C=C–H, cis to Py), 5.31 (m, Py–C=C–H, trans to Py), and 2.23 (m, CH_3). Weak couplings (0.5–1.5 Hz) were noted between geminal vinylic protons and between the vinylic and methyl protons.

A sample of 2-isopropenylpyridine (**13**) was prepared by heating 2-isopropylpyridine (5.63 g, 46.6 mmol) with *N*-bromosuccinimide (9.3 g, 46.6 mmol) in CCl_4 until complete consumption of the NBS. Filtration of the suspension and removal of the solvent and remaining 2-isopropyl pyridine (*in vacuo*) from the filtrate gave the crude bromo derivative, which was dissolved in anhydrous THF and treated with 1 equiv of potassium *tert*-butoxide at 0°. Usual work-up, according to that employed for the dehydrohalogenation of the *x*-(3-chloropropyl)pyridines, provided **13**.

2-(2-Chloropropyl)pyridine (14): Since **14** was contaminated with some **12**, only the saturated CH signals are pertinent: nmr δ 4.60 (sextet, –CHCl–, J = 6.8 Hz), 3.10 (d, $-CH_2-$, J = 6.8 Hz), and 1.47 (d, $-CH_3$, J = 6.8 Hz).

Treatment of a sample of **14** with potassium *tert*-butoxide in THF (*vide supra* for procedure) yielded only **12**.

2-(1-Chloro-2-propyl)pyridine (15): Although **15** was admixed with some **13**, the saturated CH signals served for identification: nmr δ 3.82 (q, $-CH_2Cl$, J = 6.8 Hz), 3.17 (sextet, CH, J = 6.8 Hz), and 1.33 (d, $-CH_3$, J = 6.8 Hz). That the diastereotopic methylene protons appear as a quartet is understandable; however, the diastereotopic methylene protons in **14** appear as a doublet. Nevertheless, the chemical shifts observed for the protons in **15** and in **14** correspond rather closely to calculated CH shifts for 1-chloro-2-phenylpropane and 2-chloro-1-phenylpropane, respectively. The calculated shifts were based upon values derived from known phenyl derivatives.[18]

B. 4-Cyclopropylpyridine (16). The reaction products from **16** and aluminum chloride had a marked tendency to change into a water-soluble gummy mass, so the exact proportion of components could not be obtained. However, analogous to **10**, the preponderant product was *trans*-4-propenylpyridine (**17**) and the minor products were the 4-isopropenyl-(**18**) and the corresponding 4-(chloropropyl)pyridine derivatives: *trans*-4-propenylpyridine, nmr δ 6.30 (m, Py–CH=CH–), 1.77 (d, CH_3, J = 5.0 Hz); 4-isopropenylpyridine (trace); 4-(2-chloropropyl)pyridine (**19**), nmr δ 4.27 (sextet, –CHCl–, J = 7.0 Hz), 2.90 (d, Py–CH_2–, J = 7.0 Hz), and 1.43 (d, CH_3, J = 7.0 Hz); 4-(1-chloro-2-propyl)pyridine (**20**), nmr δ 3.67 (d, $-CH_2Cl$), 2.90 (sextet, –CH–), and 1.24 (d, CH_3, J = 7.0 Hz).

Reaction of *trans*-2-Propenylpyridine with Anhydrous Aluminum Chloride. A solution of **12** (325 mg, 3.73 mmol) and anhydrous aluminum chloride (728 mg, 7.46 mmol) in 20 ml of CH_2Cl_2 was refluxed for 12 hr and worked up in the manner described for the cyclopropylpyridine–aluminum chloride reactions. By nmr analysis the product was shown to be a 9:1 mixture of starting material and 2-(2-chloropropyl)pyridine(**14**).

In contrast, passing dry HCl gas into a solution of **12** in CH_2Cl_2 for 2 hr or treating **12** with 12 *N* HCl led upon treatment with aqueous $NaHCO_3$ solution to unchanged **12**.

Attempted Cleavage Reactions of 2-Cyclopropylpyridine. The cyclopropane ring in **10** was inert to (a) treatment with 12 *N* HCl at 25° for 12 hr; (b) treatment with 36 *N* H_2SO_4 at 25° for 3 hr; (c) irradiation in dry benzene at 254 nm (low-pressure mercury lamps) for 40 hr or in cyclohexane for 20 hr; and (d) heating under nitrogen in a sealed tube at 315° for 12 hr.

2-Cyclopropylpyridine methiodide was thermally inert at 200° after 12 hr; at 300° it dissociated into **10** and CH_3I.

At 400° 2-cyclopropylpyridine underwent deep-seated decomposition after 3 hr to yield acetylene and ethylene (mass spectrum), 2-picoline, 2-*n*-propylpyridine, and a brittle, shiny black solid that contained nitrogen (by combustion, a $C_{12}H_7N$ ratio) and was insoluble in $CHCl_3$, EtOH, or CF_3COOH. The 2-picoline and 2-*n*-propylpyridine[19] were identified by nmr and vpc comparisons with authentic samples.

By comparison, 4-cyclopropylpyridine darkened after a 2-hr heating period to 400°, but no new gaseous or liquid component was detected. Spectral and chromatographic analyses showed only unchanged **16**.

Reaction of 3-Allylpyridine (22) with Anhydrous Aluminum Chloride. A solution of **22** (1.6 g, 13.5 mmol, distilled from barium oxide) and anhydrous aluminum chloride (3.6 g, 27 mmol) in 50 ml of CH_2Cl_2 was refluxed for 12 hr and worked up in the usual way. The 1.8 g of sweet-smelling liquid was shown by nmr analysis to be a mixture of *trans*-3-propenylpyridine (**21**) and 3-(2-chloropropyl)pyridine (**23**), nmr (neat) δ 4.21 (sextet, –CHCl–, J = 6.5 Hz), 2.90 (d, $-CH_2$, J = 6.5 Hz), and 1.39 (d, $-CH_3$, J = 6.5 Hz), in a 1.64:1.0 ratio.

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Registry No.—**1**, 52225-85-1; **2**, 17944-57-9; **3**, 21011-66-5; **3** picrate, 52225-86-2; **4**, 5264-02-8; **5**, 2859-68-9; **6**, 52225-87-3; **7**, 2859-67-8; **8**, 2629-72-3; **10**, 20797-87-9; **10** picrate, 41764-98-1; **11**, 52225-88-4; **12**, 52248-74-5; **13**, 6515-13-5; **14**, 52225-89-5; **15**, 52225-90-8; **16**, 4904-21-6; **16** picrate, 21011-78-9; **17**, 52248-75-6; **18**, 17755-30-5; **19**, 52225-91-9; **20**, 52225-92-0; **21**, 52248-76-7; **21** picrate, 52248-77-8; **22**, 7300-28-9; **23**, 52225-93-1; $AlCl_3$, 7446-70-0.

References and Notes

(1) J. J. Eisch and D. A. Russo, *J. Organometal. Chem.*, **14**, P13 (1968).
(2) Subsequent to our work, H. Pines, *et al.*, *J. Org. Chem.*, **36**, 2304, 2308 (1971), encountered such intramolecular cyclizations in the reactions of alkenylpyridines with alkali metal catalysts.
(3) A. P. Gray and H. Kraus, *J. Org. Chem.*, **31**, 399 (1966).
(4) A. Burger, D. G. Markees, W. R. Nes, and W. L. Yost, *J. Amer. Chem. Soc.*, **71**, 3307 (1949).
(5) R. Levine and G. R. Patrick, *J. Org. Chem.*, **38**, 3942 (1973).
(6) O. G. Lowe and L. C. King, *J. Org. Chem.*, **24**, 1200 (1959).

(7) J. J. Eisch and D. A. Russo, unpublished studies.
(8) R. G. Bergman and W. L. Carter, *J. Amer. Chem. Soc.*, **91**, 7411 (1969).
(9) R. Damico and C. D. Broaddus, *J. Org. Chem.*, **31**, 1607 (1966).
(10) P. S. Skell and S. R. Sandler, *J. Amer. Chem. Soc.*, **80**, 2024 (1958).
(11) H. Hart and R. H. Schlosberg, *J. Amer. Chem. Soc.*, **88**, 5030 (1966).
(12) H. Hart, R. H. Schlosberg, and R. K. Murray, Jr., *J. Org. Chem.*, **33**, 3800 (1968).
(13) F. Joy, M. F. Lappert, and B. Prokai, *J. Organometal. Chem.*, **5**, 506 (1966).
(14) J. J. Eisch and L. J. Gonsior, *J. Organometal. Chem.*, **8**, 53 (1967).
(15) J. J. Eisch and W. C. Kaska, *J. Amer. Chem. Soc.*, **88**, 2213, 2976 (1966).
(16) K. C. Kennard and D. M. Burness, *J. Org. Chem.*, **24**, 464 (1959).
(17) R. P. Mariella and K. H. Brown, *J. Org. Chem.*, **34**, 3191 (1969).
(18) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1959, pp 53–58.
(19) In a modification of the procedure of K. Ziegler and H. Zeiser [*Justus Liebigs Ann. Chem.*, **485**, 174 (1931)], 2-picolyllithium in ethyl ether was allowed to react with ethyl iodide.

Rearrangement of Anhydropyrimidine Nucleosides in Liquid Hydrogen Fluoride. Mechanism, Scope, and Synthetic Studies

Joseph O. Polazzi, David L. Leland, and Michael P. Kotick*

Molecular Biology Department, Miles Laboratories, Inc., Elkhart, Indiana 46514

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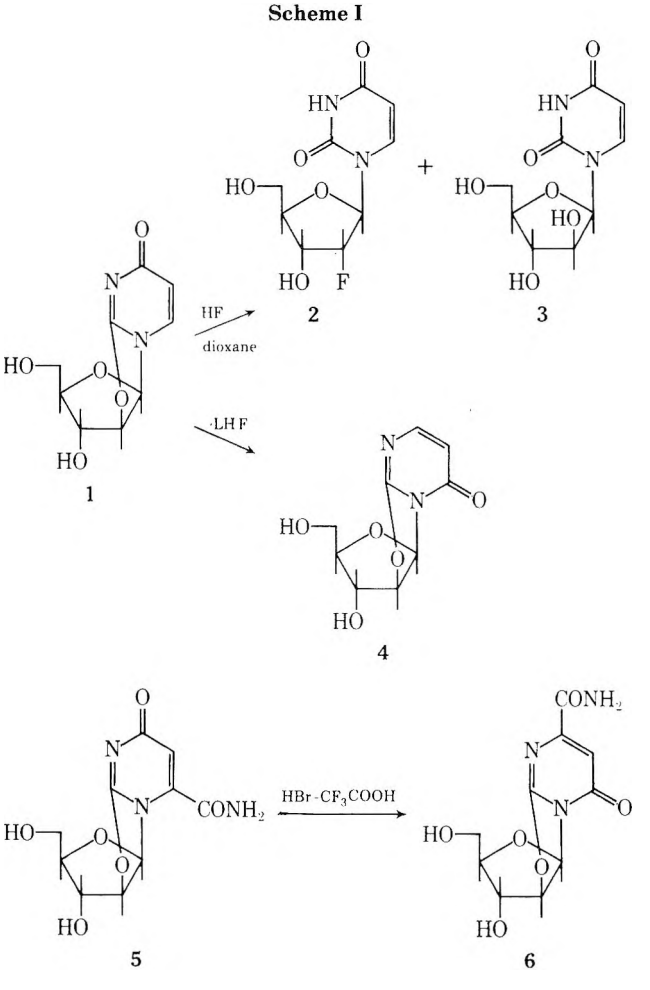
In contrast to the reaction of 2,2′-anhydro-1-β-D-arabinofuranosyluracil (1) with HF in dioxane which yields 2′-fluoro-2′-deoxyuridine (2), liquid hydrogen fluoride treatment of 1 resulted in rearrangement of the nucleosidic bond from N-1 to N-3. The mechanism proposed to account for the formation of 2,2′-anhydro-3-β-D-arabinofuranosyluracil (4) involves N-1–C-1′ bond cleavage of the protonated anhydro nucleoside with the formation of a resonance-stabilized carbonium ion in the carbohydrate portion of the molecule. Re-formation of the nucleosidic bond by electrophilic attack yields the thermodynamically more stable N-3 isomer. Other 2,2′-anhydropyrimidine nucleosides underwent similar rearrangement in liquid hydrogen fluoride, but 2,3′ and 2,5′-anhydro compounds were cleaved to the heterocyclic base. Cleavage of the anhydro bond of the rearranged nucleoside by aqueous base treatment yielded 3-β-D-arabinofuranosylpyrimidines. The di-*O*-benzoyl derivative of **4** (**20b**) served as a useful intermediate for the preparation of 3-β-D-ribofuranosyluracil (**21**) and 2′-deoxy-3-β-D-ribofuranosyluracil (**24**).

Aqueous acid or base hydrolysis of 2,2′-anhydropyrimidine nucleosides results in cleavage of the anhydro bond at C-2 of the pyrimidine nucleus with the formation of arabinosyl nucleosides.[1] In contrast, treatment of 2,2′-anhydro nucleosides under anhydrous conditions with hydrogen halides yields 2′-halogeno-2′-deoxyribofuranosylpyrimidine nucleosides. In this manner, 2′-chloro- and 2′-bromo-2′-deoxyuridine[2] have been obtained by reaction of 2,2′-anhydrouridine (**1**) with HCl in dioxane or HBr in trifluoroacetic acid, respectively. 2′-Chloro- and 2′-bromo-2′-deoxycytidine have been prepared from 2,2′-anhydrocytidine by reaction with hydrogen halides in DMF.[3] Treatment of **1** with hydrogen fluoride in dioxane solution gives 2′-fluoro-2′-deoxyuridine (**2**) in moderate yield.[2,4] Conflicting reports[3,5] exist as to the applicability of the HF–dioxane method for the preparation of the 2′-fluoro-2′-deoxy analog of cytidine from 2,2′-anhydrocytidine. The preparation of 2′-fluoro-2′-deoxycytidine from **2** by standard synthetic sequences has been reported.[4]

Fluorinated nucleoside **2** is desired in our laboratory as a precursor for the preparation of the corresponding 2′-fluorinated pyrimidine polynucleotides.[6,7] However, our large-scale preparations of **2**, which are carried out essentially as reported,[2,4] contain a 3:2 ratio of **2** and 1-β-D-arabinofuranosyluracil (**3**). Nucleoside **3** is derived from **1** by hydrolytic cleavage, presumably from traces of moisture which are introduced into the mixture of **1** and dioxane during the addition of liquid hydrogen fluoride. Although **2** can readily be separated from **3** by acetylation[4] of the reaction products, our attempts to improve the yield of **2** were not successful. We therefore explored the reaction of **1** with neat liquid hydrogen fluoride (LHF) (Scheme I).

Scheme I

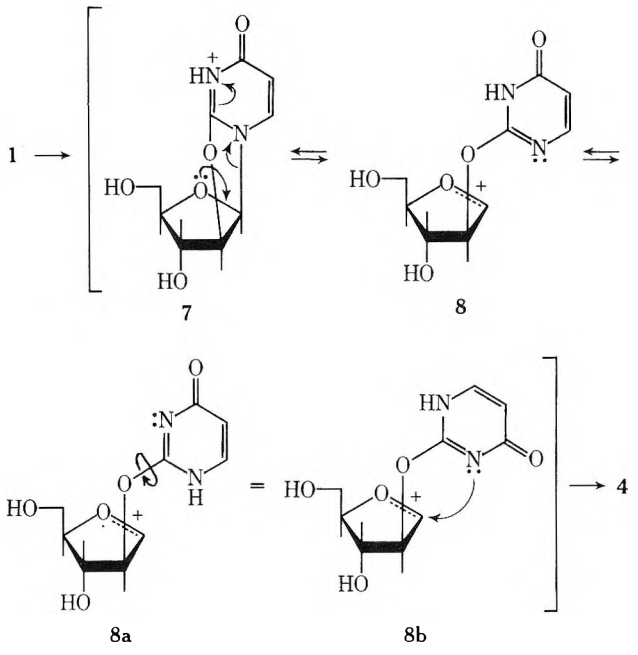


Treatment of **1** with LHF at elevated temperatures unexpectedly resulted in rearrangement of the nucleosidic linkage from N-1 of the uracil ring to N-3, with retention of the anhydro bond, to yield 2,2′-anhydro-3-β-D-arabinofuranosyluracil (**4**). We have previously reported the proof of structure of this novel pyrimidine anhydro nucleoside.[8] The analogous rearrangement of 2,2′-anhydro-1-β-D-arabi-

nofuranosyluracil-6-carboxamide(**5**) to the N-3 isomer **6**, on treatment with trifluoroacetic acid saturated with HBr, has also been reported.[9] In view of the novelty of the 2,2′anhydro-N-3-pyrimidine nucleosides prepared by this rearrangement, we have further studied the mechanism and scope of the LHF-induced rearrangement as well as some synthetic transformations in this series of pyrimidine nucleosides. This report is concerned with the results of these studies.

Mechanism. The mechanism by which **1** rearranges to **4** in superacid media[10,11] is of interest in view of the reported facile cleavage of nucleosidic bonds in LHF.[12] Upon dissolution of **1** in LHF, protonation of the uracil nucleus occurs to give **7** (Scheme II). Pyrimidine anhydro nucleosides are known to be protonated, even by such weak acids as benzoic acid,[13] and cations of uracil and its alkylated derivatives have been observed in superacid solution.[14] Migration of the free electron pair in protonated anhydro nucleoside **7**, from N-1 into the heterocyclic ring, takes place with concurrent cleavage of the nucleosidic bond. Scission of the N-1–C-1′ bond gives rise to resonance-stabilized oxocarbonium ion **8**. A similar mechanism has been proposed for the aqueous acid catalyzed hydrolysis of the nucleosidic bond in pyrimidine nucleosides[15,16] and may also be the mechanism operative in the LHF-induced degradation of nucleosides and polynucleotides. Rotational equilibration about the LHF-stable O-2–C-2′ imino ester bond[17] then takes place. Re-formation of the nucleosidic bond from intermediates **8** occurs on cooling of the reaction mixture to give the thermodynamically more stable N-3 anhydro nucleoside **4**.

Scheme II



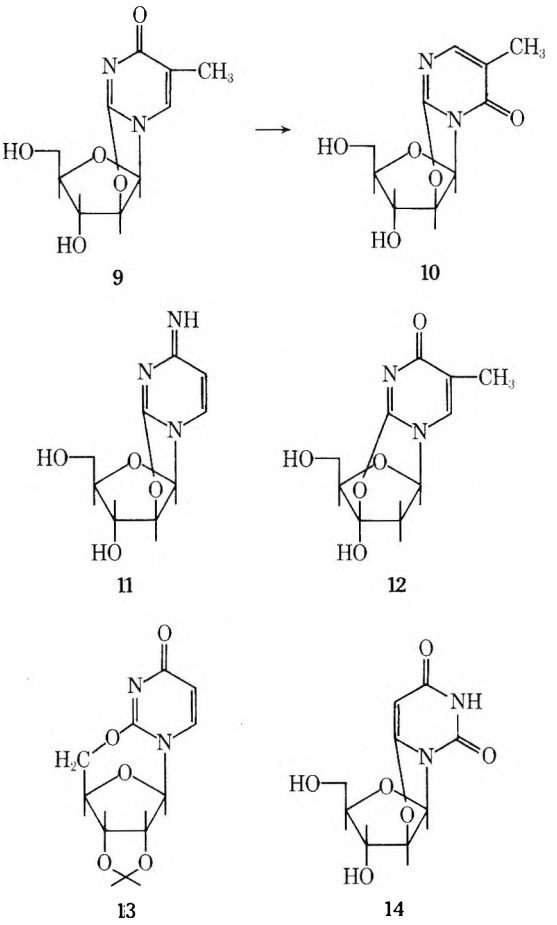
It should be noted that this mechanism differs from that proposed[18] by Tolman and coworkers for the rearrangement of **5** in HBr–CF_3COOH. In LHF, the poor nucleophilicity of fluoride ion makes displacement of the nucleosidic bond by F^- to form a glycosyl fluoride unlikely. Formation of a stabilized C-1′ carbonium ion followed by electrophilic attack of the neighboring heterocyclic ring is thus the more favored mechanism for the observed rearrangement in LHF. The uniqueness of HF–dioxane as a selective agent for the nucleophilic displacement of the anhydro bond in **1** to give **2**, in contrast to the rearrangement of **1** in LHF, is not readily apparent.

The preferential rearrangement of **1** to **4** cannot be explained on the basis of steric hindrance. An inspection of molecular models indicates that there is less steric hindrance in intermediate **8a** than in **8b** owing to the 4-oxo function. Reasons for re-formation of the nucleosidic bond from intermediate **8b** at the more hindered N-3 position, to give **4** as the major reaction product, are not evident. It has, however, been reported that diazomethane treatment of 2-methoxy-4-pyrimidone, a compound similar to cleaved intermediates **8**, results in preferential introduction of the second methyl group in the more hindered N-3 position.[19]

Thermodynamic control of the product distribution in the rearrangement of **1** to **4** has been shown by equilibration experiments (see Experimental Section for details). Treatment of either anhydro nucleoside **1** or **4**, with LHF at 80° for 18 hr, resulted in approximately the same N-1–N-3 product distribution with the N-3 isomer predominating by a ratio of approximately 7:2. It should be noted that only traces of uracil, resulting from cleavage of both the nucleosidic and anhydro bonds, were detected in these reactions. No other products could be demonstrated by tlc methods.

Scope. We have further investigated the rearrangement of some other pyrimidine anhydro nucleosides in LHF. Treatment of 2,2′-anhydro-1-β-D-arabinofuranosyl-5-methyluracil (**9**)[2] with LHF under standard conditions yielded the corresponding N-3 isomer **10** (Scheme III), in

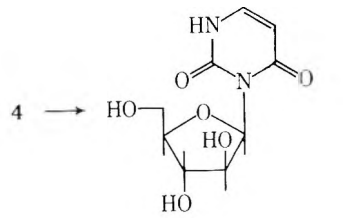
Scheme III



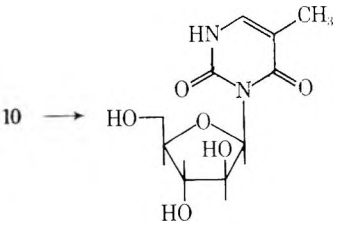
addition to traces of 5-methyluracil and unreacted starting material. The nmr spectrum of **10** clearly indicated H-1′ as a doublet with $J_{1'-2'}$ = 5.5 Hz, indicative of the cis relationship between H-1′–H-2′. Allylic coupling (J = 1.5 Hz) was observed between H-6 (δ 7.55) and the 5-methyl protons.

Thin layer chromatographic evidence indicated that

Scheme IV



15



16

2,2′-anhydro-1-β-D-arabinofuranosylcytosine hydrochloride[5] (11) underwent reaction in LHF. However, attempts to isolate the rearranged N-3 product were unsuccessful owing to slow hydrolysis of the 4-amino group as indicated by a change in tlc migration of the reaction product. Complete hydrolysis of both the amino and anhydro functions was accomplished by ammonium hydroxide treatment. Acetylation of this crude mixture with acetic anhydride–pyridine yielded an approximately equimolar mixture of tetraacetyl-1-β-D-arabinofuranosylcytosine and triacetyl-3-β-D-arabinofuranosyluracil (**17a**) as the only nucleosidic products.

Treatment of 2,3′-anhydro-1-(2′-deoxy-β-D-lyxofuranosyl)thymine (**12**)[13a] or 2′,3′-*O*-isopropylidene-2,5′-anhydro-1-β-D-ribofuranosyluracil (**13**)[20] with LHF at 80° for 18 hr resulted in cleavage of both the anhydro and nucleosidic bonds. The free pyrimidine base was isolated from these reaction mixtures in nearly quantitative yield. Polymerization of the carbohydrate portion of the molecule was indicated by the formation of a dark, water-insoluble residue. Attempts were also made to rearrange **12** and **13** under milder temperatures and/or shorter periods of time. In cases where extensive degradation of the parent anhydro nucleoside to free base did not occur, conversion of **12** or **13** to products was minimal. The nucleosidic bond in anhydro nucleosides **12** (six-membered anhydro ring) and **13** (seven-membered anhydro ring) is apparently cleaved in LHF in an analogous manner to the nucleosidic bond in the 2,2′-anhydro nucleosides (five-membered anhydro ring). However, the distance from the C-1′ carbonium ion to the heterocyclic ring nitrogens is of sufficient length to prevent reformation of the nucleosidic bond at either N-1 or N-3. Further hydrolysis of the cleaved intermediates liberates the free base. 6,2′-Anhydro-1-β-D-ribofuranosyluracil (**14**)[21] was isolated unchanged upon treatment with LHF under the usual reaction conditions. This anhydro nucleoside is reported to be relatively stable in strong acid solution.[21]

Synthetic Transformations. The anhydro bond of the 2,2′-anhydro N-3 nucleosides, **4** and **10**, was rapidly cleaved by treatment with aqueous base to yield the N-3 nucleosides, **15** and **16** (Scheme IV). The large bathochromic shift observed for **15** and **16** in alkaline solution confirm the site of the nucleosidic bond at N-3 of the uracil chromophore.[22] The assignment of the arabino configuration for **15**, and thus of **4**, was made on the basis of nmr spectroscopy. The large coupling constant (8 Hz), together with the observed downfield shift (~0.4δ)[23] of the anomeric proton from that reported[24] for the corresponding ribo nucleoside (see also below), substantiate a cis arrangement of protons at H-1′–H-2′. It is noteworthy that the anomeric proton of **15** in DMSO-d_6–D_2O solution appears as an unsymmetrical doublet as a result of virtual coupling[25] between H-1′ and H-2′–H-3′. In D_2O solution, the anomeric proton appeared as the expected doublet.

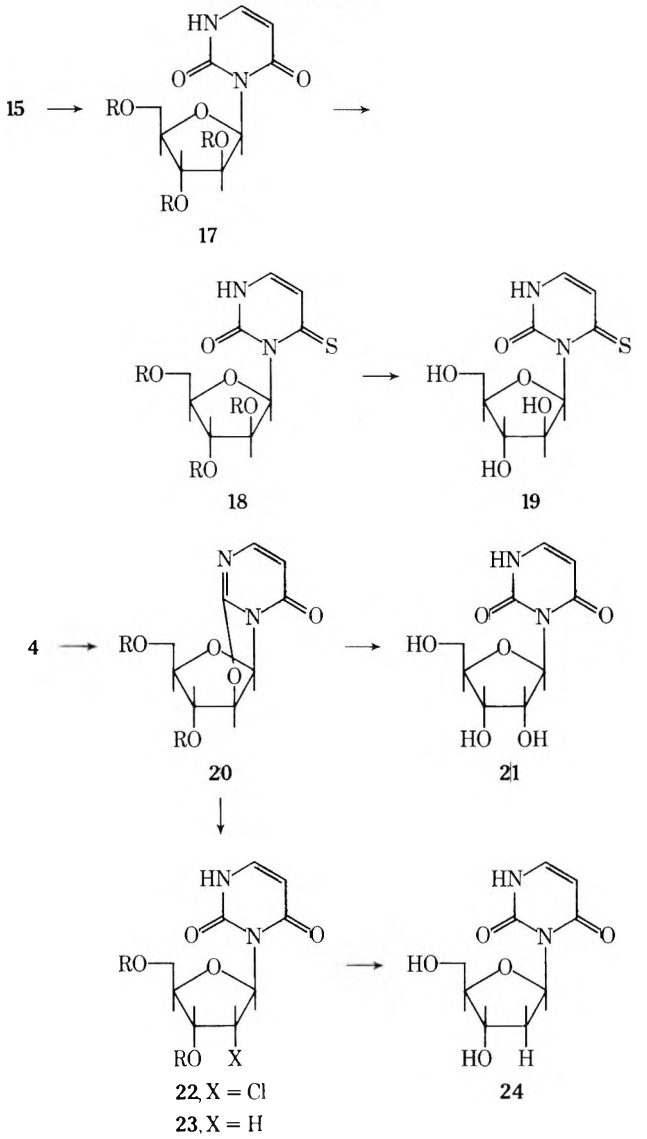
Although arabino nucleoside **15** could be isolated in crystalline form, it was more convenient to convert the syrupy hydrolysis product to crystalline acyl derivatives **17** for further synthetic transformations. Thiation of tribenzoate **17b** was smoothly effected by treatment with P_2S_5 in dioxane. Assignment of the thio group to the 4 position in **18** rests on analogy with the thiation of 3-methyluracil[26] and tri-*O*-benzoyl-3-β-D-ribofuranosyl-6-methyluracil.[27] Removal of the blocking groups by base-catalyzed methanolysis yielded the readily crystalline thioxo nucleoside **19**. The H-1′ proton signal for **19** (δ 7.51) was considerably shifted downfield from the H-1′ signal (δ 6.65) of the parent oxo nucleoside as a reflection of the magnetic anisotropy of the thione group.[28]

Conversion of thione **19** to a 4-amino derivative was attempted by reaction with methanolic or liquid ammonia under a variety of temperature conditions, or by oxidation of the thione to the sulfonate followed by reaction with aqueous ammonia.[29] Under conditions where reaction of **19** occurred (loss of starting material by tlc and uv), further work-up of these reactions resulted in regeneration of the 2,4-dioxo-N-3-substituted uracil chromophore. The inability to isolate a 4-amino compound is probably due to participation at C-4 by the 2′-*arabino*-hydroxyl group.[30] These results mirror those obtained upon rearrangement of **11** in LHF.

Reaction of **4** with acetic anhydride or benzoyl chloride in pyridine solution yielded the di-O-acylated derivatives **20** (Scheme V). Anhydro ring opening, with benzoyl participation, was effected by treatment of **20b** with boron trifluoride etherate[31] in refluxing methanol. The mixture of 2′(3′)-*ribo*-hydroxy benzoates thus obtained was further hydrolyzed to give 3-β-D-ribofuranosyluracil (**21**)[24] in moderate overall yield. It should be noted that whereas both the arabino nucleoside **15** and the ribo nucleoside **21** had the same tlc migration in chloroform–methanol solvents, these compounds were readily distinguishable by nmr and chemical means. The H-1′ proton of **21** (δ 6.26) exhibited a small H-1′–H-2′ coupling (3.5 Hz) which was further diminished upon the formation of an isopropylidene derivative.

Anhydro nucleoside **4** was converted to 2′-deoxy-3-β-D-ribofuranosyluracil (**24**) by the series of reactions described by Holý.[32] Anhydrous hydrogen chloride treatment of dibenzoate **20b** in DMF solution resulted in cleavage of the anhydro bond by nucleophilic displacement to give the 2′-chloro-2′-deoxyribo derivative **22b** as an analytically pure foam. The nmr spectrum of **22b**, in $CDCl_3$ solution, showed H-1′ (δ 6.82) as a doublet with $J_{1',2'}$ = 3.5 Hz, in contrast to the larger coupling constant ($J_{1',2'}$ = 6.0 Hz) observed for the H-1′ proton (δ 6.65) of **20b**, indicating inversion at C-2′ to the ribo configuration. In addition, the C-2′ proton (δ 5.42) was observed as an unsymmetrical quartet with $J_{2',3'}$ = 7.0 Hz. Hydrogenolysis of the 2′-chloro function in **22b** was smoothly effected by use of tri-*n*-butyltin hydride in refluxing benzene solution in the presence of a free-radical initiator to give the 2′-deoxy benzoylated nucleoside **23b** in pure crystalline form after chromatography. The H-1′ proton of **23b** was observed in $CDCl_3$ as an unsymmetrical quartet (δ 6.93, $J_{1',2',2''}$ = 4 and 8 Hz, $W_{1/2}$ = 13.5 Hz) in contrast to the expected pseudo-triplet.[33] Similar excep-

Scheme V



a series, R = $COCH_3$
b series, R = COC_6H_5

tions to the general rule for the assignment of anomeric configuration in 2′-deoxynucleosides have been observed.[34]

Debenzoylation of crude **23b** was smoothly accomplished by treatment with methanolic sodium methoxide. After purification by column chromatography, 2′-deoxy-3-β-D-ribofuranosyluracil (**24**) was obtained as a crystalline solid which could not be obtained in a solvent-free state with melting point comparable to that previously reported for this compound.[35] Several recrystallizations from 2-propanol, the reported crystallization solvent, did not give analytically pure material, although our product migrated as a single spot on tlc and had the reported spectroscopic characteristics.

It should be noted that attempts to apply the LHF-induced migration of nucleosidic bonds to the more acid-labile purine series were unsuccessful. Treatment of 8,2′-anhydro-8-oxo-9-β-D-arabinofuranosyladenosine with LHF resulted in a nearly quantitative recovery of 8-oxoadenine.

Experimental Section

General Procedures. Melting points were determined with a Thomas-Hoover apparatus (capillary method) and are uncorrected. Ultraviolet spectra were recorded on a Cary Model 15 spectrometer using previously reported procedures[6a] and nuclear magnetic resonance spectra were measured with a Varian A-60D (Sadtler Laboratories, Philadelphia, Pa.) or a Varian T-60A spectrometer in the solvents indicated with TMS or DSS as an internal standard. Values given for coupling constants (hertz) and chemical shifts (δ) are first order. Thin layer chromatographic separations were carried out on microscope slides (1 × 3 or 2 × 3 in.) coated with thin layers (0.25 mm) of silica gel GF-254 (EM reagents). Materials were detected with uv light and/or charring after spraying with 20% sulfuric acid in ethanol. Preparative column chromatographic separations were carried out over silica gel G (EM reagents) by a described method.[36] Evaporations were carried out under reduced pressure with bath temperatures below 45°. Microanalyses were performed by Research Division Analytical Services, Miles Laboratories, and by Galbraith Laboratories, Inc., Knoxville, Tenn.

General Procedures for Reactions with Liquid Hydrogen Fluoride. The hydrogen fluoride utilized in these experiments was obtained from Matheson Gas Products and was 99.9% minimum liquid phase purity. The desired amount of LHF was poured out of an inverted tank as directed[37] into plastic cylinders and then poured into a precooled (5°) Monel (40 ml) or stainless steel (200 ml) autoclave. The sealed autoclave was heated in a thermostated oil bath for the indicated time period. After cooling in ice, the autoclave was opened and the dark contents were poured into a plastic beaker. With magnetic stirring, the LHF was evaporated with the aid of a stream of warm air from a blower. The dark residue was dissolved in water and the solution was neutralized by the addition of solid calcium carbonate. Ethanol was added at intervals to control the foaming. The resulting neutral suspension was treated with charcoal, warmed on the steam bath, and filtered through Celite. The filtrate was further processed as described below.

2,2′-Anhydro-3-β-D-arabinofuranosyluracil (4). A mixture of **1**[38] (10.0 g, 44.6 mmol) and LHF (100 ml) was heated at 80° for 18 hr. The aqueous filtrate, obtained after neutralization of the reaction mixture, was evaporated to a thick syrup which was not allowed to crystallize, but was dissolved in chloroform–methanol and chromatographed on silica gel (1 kg) using 5:1 chloroform–methanol as the eluent. Fractions containing the desired product were combined, evaporated, and azeotroped with ethanol to give a foam. Crystallization of the foam was effected from a small amount of methanol with the addition of chloroform. After cooling overnight, the crystals were collected, washed with methanol–chloroform followed by chloroform, and dried at 60° to give 3.76 g of **4**, mp 144–146°. A second crop of material (1.57 g) with mp 144–146° was obtained by further processing of the mother liquor. The overall yield of **4** was 5.33 g (53%).

Material prepared in another reaction was recrystallized from methanol–chloroform to give an analytical sample of 2,2′-anhydro-3-β-D-arabinofuranosyluracil (**4**): mp 144–146°; λ_{max} (pH 2, 7) 271 nm (ε 6900), λ_{min} (pH 2, 7) 233 (900), λ_{max} (pH 12) 272 (6800), λ_{min} (pH 12) 235 (1100); nmr (DMSO-d_6) δ 7.73 (1 H, d, H-6), 6.48 (1 H, d, H-1′), 6.02 (1 H, d, H-5, J_{6-5} = 7 Hz), 5.82 (1 H, d, 3′-OH, $J_{3'-3'OH}$ = 4.5 Hz, exchanges with D_2O), 5.21 (1 H, d, H-2′, $J_{1'-2'}$ = 5.5 Hz), 4.86 (1 H, t, 5′-OH, $J_{5'A-5'B-5'OH}$ = 5.5 Hz, exchanges with D_2O), 4.47 (1 H, m, H-3′), 4.12 (1, m, H-4′), 3.35 (2 H, m, H-5′A, -5′B, changes to d with J = 4.5 Hz on D_2O addition).

Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.38. Found: C, 47.72; H, 4.36; N, 12.25.

Equilibration Experiments. The appropriate anhydro nucleoside, **1** or **4** (0.10 g), was treated with LHF (10 ml) at 80° for 18 hr. After work-up in the usual manner, the resulting aqueous solution was evaporated to a syrup which dissolved in methanol. A portion of this methanolic solution was applied to 2 × 3 in. thin layer slides and the slides were developed with 6:1 chloroform–methanol. In this system, the products were cleanly separated and have the following R_f values: uracil (0.6), **4** (0.5), **1** (0.3). The uv-absorbing bands were scraped from the plates and eluted from the gel with water. The absorbance was determined *vs.* an appropriate blank portion of the plate. The percentage distribution of the products, averaged from two plates, was determined by ultraviolet spectroscopy using the reported extinction coefficients.

	Product distribution, %		
Starting Material	1	4	Uracil
1	20	74	6
4	22	73	5

2,2′-Anhydro-3-β-D-arabinofuranosyl-5-methyluracil (10). A mixture of **9** (1.80 g, 7.5 mmol) and LHF (25 ml) was heated in a Monel autoclave for 18 hr at 85°. The mixture was worked up as

described above to give a syrup which was chromatographed on silica gel (200 g) using 5:1 chloroform–methanol as the developing solvent. The fractions containing the desired product were combined and evaporated to give crystalline **10** (0.80 g, 44%). Recrystallization from ethanol gave an analytical sample of **10**: mp 180–181°; λ_{max} (pH 2, 7) 274 nm (ϵ 6900), λ_{min} (pH 2, 7) 238 (1300), λ_{max} (pH 12) 275 (6900), λ_{min} (pH 12) 239 (1500); nmr (DMSO-d_6) δ 7.55 (1 H, d, H-6, J = 1.5 Hz, coupled to CH_3), 6.39 (1 H, d, H-1′), 5.69 (1 H, d, OH-3′, $J_{3'\text{-OH-}3'\text{-H}}$ = 4.5 Hz, exchanges on addition of D_2O), 5.15 (1 H, d, H-2′, $J_{1'-2'}$ = 5.5 Hz), 4.85 (1 H, t, OH-5′, $J_{5'\text{-OH-}5'\text{A-}5'\text{B}}$ = 5.5 Hz, exchanges on addition of D_2O), 4.37 (1 H, m, H-3′), 4.04 (1 H, m, H-4′), 3.28 (2 H, m, H-5′A, -5′B, changes to d with J = 5 Hz on addition of D_2O), 1.87 (3 H, s with shoulder, methyl protons).

Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 50.18; H, 4.93; N, 11.64.

3-β-D-Arabinofuranosyluracil (15). A solution of **4** (2.00 g, 8.8 mmol) in 1 *N* sodium hydroxide (40 ml) was stirred at room temperature for 30 min and then deionized by the addition of Dowex-50 H^+. After removal of the resin by filtration, the filtrate was evaporated and the residue was azeotroped with ethanol until a foam was obtained. The foam was taken up in boiling ethyl acetate (250 ml) with the addition of ethanol (25 ml). Storage of this solution in the cold overnight gave crystalline **15** (1.32 g, mp 172–174°). An additional crop (0.61 g, mp 172–174°) was obtained on evaporation of the mother liquor to give **15** in 90% overall yield. Recrystallization from ethyl acetate–ethanol gave analytically pure **15**: mp 172.5–174°; λ_{max} (pH 2) 263 nm (ϵ 7600), λ_{min} (pH 2) 231 (1700), λ_{max} (pH 12) 292 (10,400), λ_{min} (pH 12) 247 (700); nmr (D_2O) δ 7.47 (1 H, d, H-6), 6.65 (1 H, unsymmetrical d, H-1′, $J_{1'-2'}$ = 8.0 Hz), 5.80 (1 H, d, H-5, J_{5-6} = 8.0 Hz), 4.70 (4 H, s, exchangable protons), 4.70–4.40 (2 H, m, H-2′, H-3′), 4.04–3.74 (3 H, m, H-4′, H-5′A, -5′B).

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.27; H, 4.95; N, 11.47. Found: C, 44.31; H, 4.88; N, 11.26.

3-β-D-Arabinofuranosyl-5-methyluracil (16). A solution of **10** (413 mg, 1.7 mmol) in 1 *N* sodium hydroxide (10 ml) was stirred at room temperature for 75 min and then deionized by the addition of Dowex-50 H^+. After filtration from the resin, the filtrate was evaporated to a syrup and azeotroped with ethanol to give a foam (426 mg). The foam was dissolved in hot ethyl acetate and the solution was decanted from some insoluble material. The ethyl acetate solution, on cooling overnight, gave crystals of **16** (261 mg, 59%), sinters at 105°, melts at 216–218°. Recrystallization from ethyl acetate gave pure **16**: mp 215–216.5°; λ_{max} (pH 2) 269 nm (ϵ 7100), λ_{min} (pH 2) 241 (1600), λ_{max} (pH 7) 269 (7100), λ_{min} (pH 7) 236 (1600), λ_{max} (pH 12) 299 (9400), λ_{min} (pH 12) 251 (700); nmr (D_2O) δ 7.30 (1 H, d, H-6, $J_{6\text{-}CH_3}$ = 1.5 Hz), 6.66 (1 H, unsymmetrical d, H-1′, $J_{1'-2'}$ = 8 Hz), 4.94–4.26 (6 H, m, H-2′, H-3′ and exchangeable protons), 3.87 (3 H, m, H-4′, 5′A, -5′B), 1.81 (3 H, narrow d, methyl protons).

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.56; H, 5.55; N, 10.59.

2′,3′,5′-Tri-*O*-acetyl-3-β-D-arabinofuranosyluracil (17a). From 15. A Mixture of **15** (489 mg, 2 mmol) and acetic anhydride (0.7 ml, 7 mmol) in dry pyridine (10 ml) was stirred overnight at room temperature. The mixture was evaporated and azeotroped with aqueous ethanol followed by ethanol until crystals formed. The crystals were collected to give **17a** (574 mg, 78%), mp 165–166.5°.

From 4. Anhydro nucleoside **4** (1.00 g, 4.4 mmol) was hydrolyzed in 1 *N* sodium hydroxide (20 ml) for 30 min. The solution was deionized by the addition of Dowex-50 H^+ and, after filtration from the resin, evaporated to a foam. The foam was azeotroped several times with dry pyridine and finally dissolved in dry pyridine (20 ml) and treated with acetic anhydride (1.8 ml, 19 mmol) overnight at room temperature. Work-up as above gave **17a** as a crystalline solid (1.34 g, 82%), mp 164–166°. Recrystallization from ethanol gave analytically pure **17a**: mp 166–167°; λ_{max} (pH 2) 263 nm (ϵ 7300), λ_{min} (pH 2) 231 (1300), λ_{max} (pH 12) 294 (10,100), λ_{min} (pH 12) 247 (500); nmr (DMSO-d_6) δ 10.75 (1 H, broad s, NH, exchanges on addition of D_2O), 7.48 (1 H, m, H-6, on addition of D_2O becomes a doublet, J_{6-5} = 7.5 Hz), 6.78 (1 H, d, H-1′, $J_{1'-2'}$ = 7.5 Hz), 6.03–5.40 (3 H, complex m, H-2′, H-3′, H-5; after D_2O addition, H-5 is a doublet at 5.65), 4.40–4.00 (3 H, complex m, H-4′, -5′A, -5′B), 2.12–1.86 (9 H, three sharp singlets for acetate protons).

Anal. Calcd for $C_{15}H_{18}N_2O_9$: C, 48.65; H, 4.90; N, 7.56. Found: C, 48.83; H, 4.98; N, 7.36.

2′,3′,5′-Tri-*O*-benzoyl-3-β-D-arabinofuranosyluracil (17b). The foam resulting from the hydrolysis of **15** (5.00 g, 22 mmol) was azeotroped with portions of dry pyridine and finally dissolved in pyridine (75 ml), cooled, and treated dropwise with benzoyl chloride (12.4 g, 88 mmol). Stirring was continued overnight at room temperature. Addition of ice was followed by evaporation of the pyridine and dilution of the residue with methylene chloride. The methylene chloride solution was washed successively with water, sodium bicarbonate solution, water, 2 *N* HCl, and water. After drying ($MgSO_4$), the organic solution was evaporated to a foam which crystallized on trituration with benzene. The crystals were collected to give **17b** (11.55 g, 82%), mp 108–111°. The benzene solvate of **17b**, mp 112–114°, was obtained on recrystallization from benzene: nmr (DMSO-d_6) δ 8.12–7.21 (22 H, complex, benzoyl H's, benzene, H-6), 7.08 (1 H, d, H-1′, $J_{1'-2'}$ = 8 Hz), 6.64–6.02 (2 H, complex, H-2′, H-3′), 5.61 (1 H, d, H-5, J_{5-6} = 7.5 Hz), 4.85–4.53 (3 H, m, H-4′, 5′A, -5′B).

Anal. Calcd for $C_{30}H_{24}N_2O_9 \cdot C_6H_6$: C, 68.13; H, 4.76; N, 4.41. Found: C, 67.80; H, 4.73; N, 4.42.

2′,3′,5′-Tri-*O*-benzoyl-3-β-D-arabinofuranosyl-4-thiouracil (18b). To a solution of **17b** (11.00 g, 17 mmol) in warm dioxane (200 ml) was added phosphorus pentasulfide (8.9 g, 40 mmol) and the mixture was refluxed for 3.5 hr. The hot solution was filtered through glass wool and the filtrate was evaporated to a syrup. The residual syrup was triturated with water and finally dissolved in chloroform. After washing of the organic solution three times with brine, the dried ($MgSO_4$) chloroform solution was evaporated to a syrup and dissolved in methanol. The crystals which formed were collected to give a quantitive yield of **18b**, mp 180–186°, which migrated as a single spot on tlc. Several recrystallizations of a portion of this material gave the hemimethanolate (presence of methanol confirmed by nmr) of **18b** as yellow plates: mp 195–197°; nmr (DMSO-d_6) δ 11.66 (1 H, broad s, NH, exchanges on addition of D_2O), 8.20–7.16 (17 H, benzoyl H's, H-6, H-1′), 6.54–6.13 (3 H, H-5, H-2′, H-3′), 4.94–4.50 (3 H, m, H-4′, -5′A, -5′B), 4.02 (CH_3OH).

Anal. Calcd for $C_{30}H_{24}N_2O_8S \cdot 0.5CH_3OH$: C, 62.26; H, 4.45; N, 4.76. Found: C, 62.27; H, 4.15; N, 4.66.

3-β-D-Arabinofuranosyl-4-thiouracil (19). A suspension of **18b** (1.20 g, 2.0 mmol) in methanol (20 ml) was adjusted to pH ~ 12 (moist pH paper) by the addition of 1 *M* sodium methoxide in methanol. The clear yellow solution which resulted was stirred for 1 hr, after which the reaction mixture was deionized by the addition of Dowex-50 H^+. Removal of the resin followed by evaporation of the filtrate gave a syrup which was azeotroped extensively with ethanol until a crystalline residue formed. The crystals were dissolved in hot ethanol and filtered and the solution was evaporated to a small volume. The crystals which formed on cooling were collected to give analytically pure **19** (0.29 g, 55%): mp 166–167°; λ_{max} (pH 2) 334 nm (ϵ 11,700), λ_{min} (pH 2) 286 (3000), λ_{max} (pH 12) 348 (13,600), λ_{min} (pH 12) 282 (2200); nmr (DMSO-d_6 with D_2O) δ 7.51 (1 H, d, H-1′, $J_{1'-2'}$ = 8 Hz), 7.23 (1 H, d, H-6), 6.48 (1 H, d, H-5, J_{5-6} = 7.5 Hz), 4.60–3.40 (9 H).

Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.54; H, 4.65; N, 10.77. Found: C, 41.52; H, 4.74; N, 10.75.

3′,5′-Di-*O*-acetyl-2,2′-anhydro-3-β-D-arabinofuranosyluracil (20a). A solution of **4** (500 mg, 2.2 mmol) in dry pyridine (10 ml) was treated with acetic anhydride (0.56 ml, 5.6 mmol) for 18 hr at room temperature. After the addition of ethanol, the solvents were removed and the residue was azeotroped with aqueous ethanol, followed by ethanol, until crystals formed. The crystals were collected and recrystallized from ethanol to give **20a** (528 mg, 77%): mp 112–115°; λ_{max} (pH 7) 270 nm (ϵ 6700), λ_{min} (pH 7) 233 (950); nmr (DMSO-d_6) δ 7.80 (1 H, d, H-6), 6.52 (1 H, d, H-1′), 6.08 (1 H, d, H-5, J_{5-6} = 7.0 Hz), 5.50 (1 H, d, H-2′, $J_{1'-2'}$ = 5.5 Hz), 5.34 (1 H, d, H-3′), 4.56 (1 H, m, H-4′), 4.08 (2 H, m, H-5′A, -5′B), 2.13 (3 H, s, acetate CH_3), 1.92 (3 H, s, acetate CH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_7$: C, 50.33; H, 4.55; N, 9.06. Found: C, 50.44; H, 4.49; N, 9.05.

3′,5′-Di-*O*-benzoyl-2,2′-anhydro-3-β-D-arabinofuranosyluracil (20b). A. By Use of Benzoyl Chloride. A solution of **4** (500 mg) in dry pyridine (25 ml) was treated with benzoyl chloride (0.75 ml, 6.4 mmol) at room temperature for 5 hr. After the addition of water (10 ml), the reaction mixture was evaporated to a thick syrup. The syrup was dissolved in chloroform and the chloroform solution was washed with water, saturated sodium bicarbonate solution, water, 2 *N* HCl, and water. The organic layer was dried ($MgSO_4$), filtered from salts, and evaporated to a crystalline residue. The crystals were collected and washed with ethanol to give 1.04 g of **20b** with mp 136–140°, homogeneous by tlc. Recrystallization from ethanol gave 740 mg (77%) of analytically pure **20b**, mp 156.5–157.5°.

B. By Use of Benzoyl Cyanide.[39] To a mixture of **4** (4.5 g, 20 mmol) and benzoyl cyanide (5.8 g, 44 mmol) in dimethylformamide (25 ml) was added tri-*n*-butylamine (0.2 ml). After stirring for 30 min, methanol (10 ml) was added and the reaction mixture was concentrated to a thick syrup under high vacuum. Crystallization of the syrup from ethanol followed by recrystallization of the crude product gave **20b** (6.8 g, 79%): mp 156.5–157.5°; nmr (DMSO-d_6) δ 8.27–7.30 (11 H, complex, benzoyl H's, H-6), 6.65 (1 H, d, H-1′, $J_{1'-2'}$ = 6.0 Hz), 6.09 (1 H, d, H-5, J_{5-6} = 7.5 Hz), 5.83–5.66 (2 H, m, H-2′, H-3′), 5.04–4.72 (1 H, m, H-4′), 4.60–4.33 (2 H, m, H-5′A, -5′B).

Anal. Calcd for $C_{23}H_{18}N_2O_7$: C, 63.59; H, 4.18; N, 6.45. Found: C, 63.53; H, 4.10; N, 6.31.

3-β-D-Ribofuranosyluracil (21). A mixture of **20b** (2.10 g, 4.8 mmol) and freshly distilled boron trifluoride etherate (1.1 ml, 8.7 mmol) in dry methanol (50 ml) was refluxed with the exclusion of atmospheric moisture for 2 hr. The cooled reaction mixture was evaporated to a syrup and dissolved in chloroform. After washing of the chloroform solution with saturated sodium bicarbonate followed by water, the organic layer was dried ($MgSO_4$), filtered, and evaporated to a syrup. The syrup was azeotroped several times with ethanol, dissolved in methanol (25 ml), and stirred with 1 *M* sodium methoxide in methanol (7 ml) at room temperature for 5 hr. After deionization with Dowex-50 H^+, the solution was evaporated to a semicrystalline residue. The residue was triturated with ether and the crystalline material was collected to give **21** (570 mg, 48%), homogeneous by thin layer chromatography. Recrystallization from ethanol–ether gave pure **21** (412 mg): mp 197–198° (lit.[24] mp 200–202°); nmr (D_2O) δ 7.48 (1 H, d, H-6), 6.26 (1 H, d, H-1′, $J_{1'-2'}$ = 3.5 Hz), 5.83 (1 H, d, H-5, J_{5-6} = 8.0 Hz), 4.90–4.60 (1 H, m, H-2′), 4.55–4.29 (1 H, t, $W_{1/2}$ = 12.0 Hz, H-3′, $J_{3'-2'}$ = 6.0 Hz), 4.06–3.52 (3 H, complex, H-4′, H-5′A, -5′B).

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.27; H, 4.95; N, 11.47. Found: C, 44.19; H, 4.98; N, 11.47

3′,5′-Di-*O*-benzoyl-2′-chloro-2′-deoxy-3β-D-ribofuranosyluracil (22b). A solution of **20b** (1.00 g, 2.3 mmol) in dimethylformamide (20 ml) containing HCl (1 g) was heated at 100° for 30 min. The reaction mixture was poured into water (500 ml), and the solid precipitate which formed was collected and washed well with water. The collected insoluble material was chromatographed on silica gel (100 g) using 15:1 chloroform–methanol as the eluent. Fractions containing the desired product were evaporated to give **22b** (750 mg, 69%) as a foam, homogeneous by tlc, which could not be induced to crystallize: nmr ($CDCl_3$) δ 10.03 (1 H, broad d, NH, J_{NH-6} = 6.5 Hz, exchanges on addition of D_2O), 8.20–7.12 (11 H, complex, benzoyl H's, H-6), 6.82 (1 H, d, H-1′), 5.97 (1 H, complex, H-3′), 5.76 (1 H, unsymmetrical d, H-5, J_{6-5} = 8.0 Hz), 5.42 (1 H, unsymmetrical, H-2′, $J_{1'-2'}$ = 3.5, $J_{2'-3'}$ = 7.0 Hz), 4.74–4.50 (3 H, m, H-4′, -5′A, -5′B).

Anal. Calcd for $C_{23}H_{19}ClN_2O_7$: C, 58.67; N, 4.07; N, 5.95. Found: 58.53; H, 3.85; N, 5.85.

3′,5′-Di-*O*-benzoyl-2′-deoxy-3-β-D-ribofuranosyluracil (23b). A solution of **22b** (2.00 g, 4.25 mmol), tri-*n*-butyltin hydride (4 ml), and 2,2′-azobis(2-methylproprionitrile) (40 mg) in dry benzene (50 ml) was refluxed under a nitrogen atmosphere for 3.5 hr. The reaction mixture was evaporated to dryness and the residue was triturated several times with light petroleum ether. Crystallization of the residue from benzene–hexane gave 1.64 g (88%) of crystalline material, mp 110–115°. Chromatography of a portion (1.00 g) of this material over silica gel yielded 680 mg of pure crystalline **23b**: mp 115–120°; nmr ($CDCl_3$) δ 10.13 (1 H, broad s, NH, exchanges with D_2O), 8.20–7.16 (11 H, complex, benzoyl H's and H-6), 6.93 (1 H, d of doublets, H-1′, $J_{1'-2'A}$ = 4, $J_{1'-2'B}$ = 8 Hz, $W_{1/2}$ = 13.5 Hz), 6.08–5.63 (1 H, complex, H-3′), 5.73 (1 H, d, H-5, J_{6-5} = 8 Hz), 4.82–4.42 (3 H, m, H-4′, -5′A, -5′B), 3.58–2.92 (1 H, complex, H-2′A), 2.77–2.17 (complex, H-2′B).

Anal. Calcd for $C_{23}H_{20}N_2O_7$: C, 63.30; H, 4.62; N, 6.42. Found: C, 63.62; H, 4.65; N, 6.08.

2′-Deoxy-3-β-D-ribofuranosyluracil (24). A solution of **23b** (2.00 g, 4.6 mmol) in methanol (25 ml) was made basic by the addition of 1 *M* sodium methoxide in methanol. The solution was stirred at room temperature for 6 hr, then deionized by the addition of methanol-washed Dowex-50 H^+ and filtered from the resin. The filtrate was evaporated to dryness, dissolved with water, and extracted several times with chloroform. Evaporation of the aqueous solution was followed by azeotropic distillation with ethanol to give crystalline **24** (778 mg, 74%), contaminated with traces of impurities as determined by tlc. This material was column chromatographed to give 495 mg of chromatographically pure **24**, mp 97–105°. Recrystallization from hot 2-propanol gave the hemi-2-propanolate of **24**: mp 82–90° (lit.[35] mp 169–170°); λ_{max} (pH 2) 262 nm (ϵ 7000), λ_{min} (pH 2) 231 (1600), λ_{max} (pH 7) 263 (6800), λ_{min} (pH 7) 232 (1500), λ_{max} (pH 12) 292 (9900), λ_{min} (pH 12) 248 (600). The presence of 2-propanol in this sample was confirmed by nmr spectroscopy (D_2O): δ 7.43 (1 H, d, H-5), 6.68 (1 H, unsymmetrical q, H-1′, $J_{1'-2'A}$ = 3.0, $J_{1'-2'B}$ = 8.5 Hz, $W_{1/2}$ = 16.0 Hz), 5.77 (1 H, d, H-6, J_{6-5} = 7.5 Hz), 3.13–2.65 and 2.47–1.94 (2 H, complex m, H-2′A, 2′B). All attempts to remove the 2-propanol by gradual heating under reduced pressure yielded a foam which did not give a satisfactory analysis.

Anal. Calcd for $C_9H_{12}N_2O_5 \cdot 0.5C_3H_8O$: C, 48.68; H, 6.15; N, 11.00. Found: C, 48.70; H, 6.27; N, 11.22.

Registry No.—**1**, 3736-77-4; **4**, 50664-09-0; **9**, 22423-26-3; **10**, 52259-53-7; **15**, 52305-37-0; **16**, 52259-54-8; **17a**, 50664-11-4; **17b**, 52259-55-9; **18b**, 52259-56-0; **19**, 52259-57-1; **20a**, 50664-10-3; **20b**, 52259-58-2; **21**, 6745-33-1; **22b**, 52259-59-3; **23b**, 52259-60-6; **24**, 29031-49-0.

References and Notes

(1) For leading references in reactions of pyrimidine anhydro nucleosides, see J. J. Fox, *Pure Appl. Chem.*, **18**, 223 (1968).
(2) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, 29, 558 (1964).
(3) T. Kanai, M. Ichino, and T. Nakamura, Japanese Patent 16,483 (1972); *Chem. Abstr.*, **77**, 140478b (1972).
(4) I. L. Doerr and J. J. Fox, *J. Org. Chem.*, **32**, 1462 (1967).
(5) D. H. Shannahoff and R. A. Sanchez, *J. Org. Chem.*, **38**, 593 (1973).
(6) (a) B. Janik, M. P. Kotick, T. H. Kreiser, L. F. Reverman, R. C. Sommer, and D. P. Wilson, *Biochem. Biophys. Res. Commun.*, **46**, 1153 (1972); (b) E. DeClercq and B. Janik, *Biochem. Biophys. Acta*, **324**, 50 (1973); (c) R. J. Erickson and J. C. Grosch, *Biochemistry*, **13**, 1987 (1974).
(7) S. S. Hendler, D. H. Shannahoff, and R. A.Sanchez, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, No. B-20.
(8) J. O. Polazzi and M. P. Kotick, *Tetrahedron Lett.*, 2939 (1973). A portion of this work was presented before the 168th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1974, No. CARB 58.
(9) C. V. Z. Smith, R. K. Robins, and R. L. Tolman, *J. Org. Chem.*, **37**, 1418 (1972).
(10) R. J. Gillespie, *Endeavour*, **32**, 3 (1973).
(11) J. Lenard, *Chem. Rev.*, **69**, 625 (1969).
(12) Y. Kanoaka, K. Itoh, E. Sato, A. Nomura, and Y. Mizuno, *Chem. Pharm. Bull.*, **18**, 1475 (1970); D. Lipkin, B. E. Phillips, and J. W. Abrell, *J. Org. Chem.*, **34**, 1539 (1969).
(13) (a) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963); (b) J. P. H. Verheyden, D. Wagner, and J. G. Moffatt, *ibid.*, **36**, 250 (1971).
(14) C. D. Poulter and R. B. Anderson, *Tetrahedron Lett.*, 3823 (1972).
(15) B. Capon, *Chem. Rev.*, **69**, 407 (1969).
(16) R. Shapiro and M. Danzig, *Biochemistry*, **11**, 23 (1972).
(17) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, p **664**.
(18) The mechanism proposed[9] for the rearrangement of **5** to **6** is protonation of the heterocyclic ring followed by nucleophilic attack by bromide ion on C-1′ to form an intermediate α-glycosyl bromide. Subsequent intramolecular displacement of bromide by the neighboring heterocyclic ring yields the anhydro-N-3 nucleoside **6**. The authors attribute the preferential rearrangement of **5** to **6** to steric hindrance at the N-1 position of the pyrimidine ring in the glycosyl-cleaved intermediate.
(19) J. L. Wong and D. S. Fuchs, *J. Org. Chem.*, **36**, 848 (1971).
(20) D. M. Brown, A. Todd, and S. Varadarijan, *J. Chem. Soc.*, 868 (1957).
(21) E. A. Falco, B. A. Otter, and J. J. Fox, *J. Org. Chem.*, **35**, 2326 (1970).
(22) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, 9, 199 (1952).
(23) L. B. Townsend, *Syn. Proced. Nucleic Acid Chem.*, **2**, 333 (1973).
(24) M. W. Winkley and R. K. Robins, *J. Chem. Soc. C*, 791 (1969).
(25) J. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).
(26) T. Ueda and J. J. Fox, *J. Amer. Chem. Soc.*, **85**, 4024 (1963); K. A. Watanabe, H. A. Friedman, R. J. Cushley, and J. J. Fox, *J. Org. Chem.*, **31**, 2942 (1966).
(27) R. S. Klein, I. Wempen, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **35**, 2330 (1970).
(28) R. A. Long and L. B. Townsend, *Chem. Commun.*, 1087 (1970).
(29) H. Hayatsu, *J. Amer. Chem. Soc.*, **91**, 5693 (1969); J. Hobbs, H. Sternbach, M. Sprinzl, and F. Eckstein, *Biochemistry*, **11**, 4336 (1972).
(30) Codington, Doerr, and Fox (ref 2) have shown that 2-aminopyrimidine nucleosides containing an arabinofuranosyl moiety can undergo removal of the 2-amino function through an anhydro intermediate. Such reactions are not observed in the ribofuranosyl series. See ref 34.
(31) A. Holý, *Collect. Czech. Chem. Commun.*, **38**, 423 (1973).
(32) A. Holý, *Collect. Czech. Chem. Commun.*, **38**, 428 (1973); A. Holý, *Tetrahedron Lett.*, 1147 (1973).
(33) R. U. Lemieux and M. Hoffer, *Can. J. Chem.*, **39**, 110 (1964); M. J. Robins and R. K. Robins, *J. Amer. Chem. Soc.*, **87**, 4934 (1965).
(34) J. Žemlicka, R. Gasser, J. V. Freisler, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **94**, 3213 (1974); M. J. Robins, J. R. McCarthy, R. A. Jones, and R. Mengel, *Can. J. Chem.*, **51**, 1313 (1973).
(35) M. W. Winkley, *J. Chem. Soc. C*, 1365 (1970).
(36) B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1868 (1967).
(37) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 456.
(38) A. Hampton and A. W. Nichol, *Biochemistry*, 5, 2076 (1967).
(39) A. Holý and M. Soucek, *Tetrahedron Lett.*, 185 (1971).

Bromide Ion Induced Debromination of the 5,5-Dibromo Derivatives of "4,6-Dihydroxypyrimidine" and 6-Methyluracil

Sujit Banerjee and Oswald S. Tee*

Department of Chemistry, Sir George Williams University, Montreal H3G 1M8, Quebec, Canada

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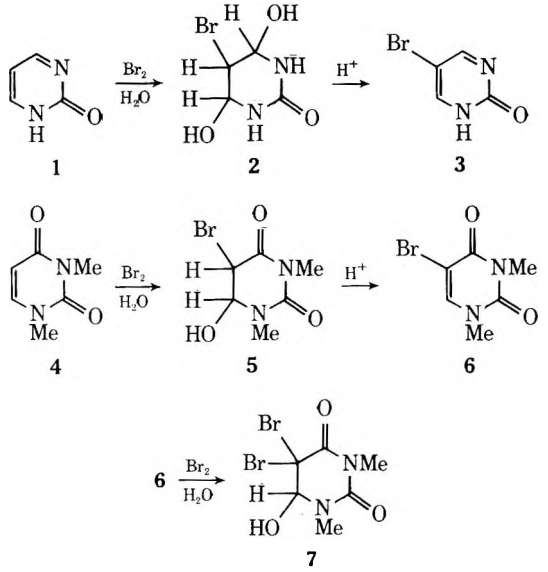
In aqueous solutions "4,6-dihydroxypyrimidine" and 6-methyluracil undergo rapid reaction with 2 molar equiv of bromine, to yield firstly their corresponding 5-bromo compounds, and secondly their 5,5-dibromo derivatives. Under acidic conditions, these latter compounds are acted upon by bromide ion to yield their monobromo derivatives and bromine. The liberated bromine is consumed in the presence of unreacted substrate to give a second equivalent of the 5-bromopyrimidinedione. The kinetics of debromination have been measured, and probable mechanisms for these processes are discussed with reference to previous studies on the dehalogenation of similar derivatives.

In an earlier study[1] we concluded that in aqueous sulfuric acid solutions the bromination at the 5 position of 2-pyrimidinone (**1**) proceeds by an addition–elimination mechanism **1** → **2** → **3**, in which acid-catalyzed deprotonation of the 5 position of **2** is the rate-determining step.[1] Similar mechanisms appear to be operative in the bromination of other pyrimidines bearing oxo and/or amino substituents at the 2 and/or 4 positions.[2] For example, 1,3-dimethyluracil (**4**) adds "HOBr" to yield the adduct **5**,[2-4] which subsequently rearomatizes to the 5-bromouracil **6** by a slow acid-catalyzed dehydration.[2] In the presence of bromine 5-bromo-1,3-dimethyluracil (**6**) forms the 5,5-dibromo derivative **7**.

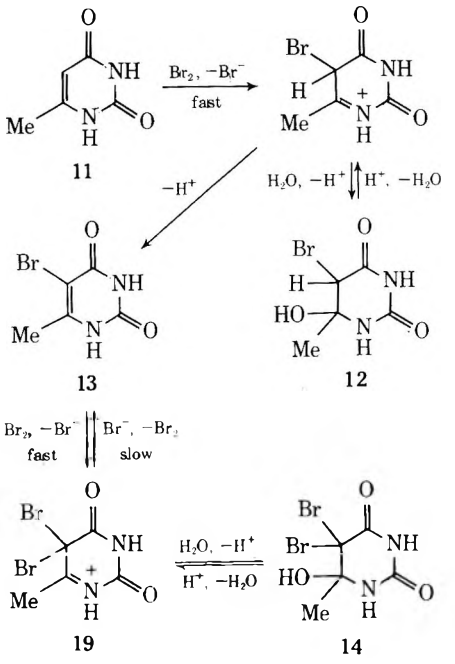


We now find that, in an analogous manner, 6-methyluracil (**11**) reacts rapidly with bromine to give, successively, **12**, **13**, and **14** (Scheme I).[5] Similarly, the reaction of "4,6-dihydroxypyrimidine" (**8**) with bromine yields a 5,5-dibromo derivative **10** *via* the 5-bromopyrimidine **9** (see Scheme II). We attempted to follow the kinetics of the brominations **8** → **9** → **10**, but obtained curious results. Subsequent experimentation revealed that these processes occur very rapidly, and that in fact the reaction we were following was the reverse reaction **10** → **9**. Similar behavior was exhibited by 6-methyluracil (**11**), and in this paper we report a kinetic study of the debrominations **10** → **9** and **14** → **13**.

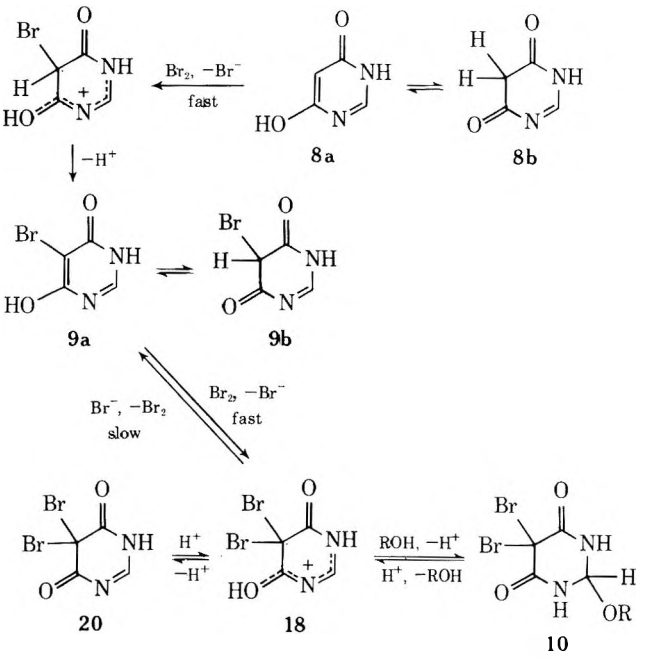
Results and Discussion

Although the major tautomeric component of "4,6-dihydroxypyrimidine" (**8**) in aqueous solutions is not known with certainty,[6] a pmr study in DMSO-d_6/D_2O solutions

Scheme I



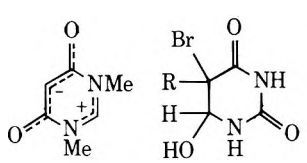
Scheme II



suggested that it exists predominantly in the enol–oxo form **8a**, with a small contribution from the dioxo form **8b**.[7] In this medium, the 5 hydrogen shows slow exchange at ambient temperatures, but the rate is greatly increased by the addition of acids or bases.[7] Similar isotopic exchange occurs with the betaine **15** in acidic D_2O solutions.[8]

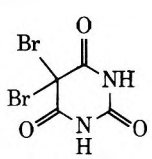
Since the acid-catalyzed exchange at the 5 position of **8** occurs more easily than that of 2-pyrimidinone (**1**)[9] or 1,3-dimethyluracil (**4**),[10] it might be anticipated that the analogous bromination of **8** would also be faster than that of **1** or **4**. Upon addition of 2 molar equiv of bromine to a solution of "4,6-dihydroxypyrimidine" (**8**) in aqueous sulfuric acid,[11] the uv absorption appropriate to **8** (λ_{max} 253 nm)[12] is removed, and the resulting solution has λ_{max} below 210 nm, with a significant tail end absorption extending beyond 240 nm. With stepwise addition of bromine, the decrease in absorbance due to **8** is accompanied by shifts to longer wavelengths, suggesting the intermediate formation of the 5-bromo derivative **9** which has λ_{max} at 261 nm. Spectrophotometric titration of **9** with bromine shows that 1 molar equiv of bromine is required for complete reaction, with isosbestic points being obtained at 215 and 240 nm. 6-Methyluracil (**11**) behaves similarly on titration with bromine, in that 2 molar equiv of bromine is required for complete removal of the absorption maximum at 261 nm,[13] and the absorbance decrease is accompanied by bathochromic shifts. Furthermore, the 5-bromo derivative **13** reacts smoothly with 1 molar equiv of bromine, as suggested by the elimination of its maximum at 276 nm and the presence of an isosbestic point at 211 nm.

Under synthetic conditions, **8** reacts with equivalent quantities of bromine in water,[14] acetic acid,[14] or methanol to give 5-bromo-"4,6-dihydroxypyrimidine" (**9**). Addition of 2 molar equiv of bromine to a methanolic suspension of **8** yields the 5,5-dibromo derivative **10** (R = Me). Attempts to isolate a similar dibromo derivative **10** (R = H) from water failed, the reaction being accompanied by extensive evolution of carbon dioxide.[15] However, pmr spectra of solutions obtained by the addition of excess bromine to a D_2O suspension of **8** or **9** show a signal at δ 6.08 attributable to the 2-H of **10** (R = H). This signal gradually decays with the appearance of other signals which are attributed to decomposition products.[15] Similar spectra were obtained on treatment of the monobromo derivative **9** with bromine. These observations, and the spectrophotometric titration data, suggest the rapid formation of the 5,5-dibromo derivative **10** (R = H). The compound **10** (R = Me) liberates iodine from solutions of potassium iodide, and in the presence of bromide ion and acid it converts **8** to the monobromopyrimidine **9**, during the course of which **10** itself is also converted to **9**. The reactivity of 5,5-dibromopyrimidine derivatives is well established, as illustrated by the facile debromination of the uracil adduct **16** (R = Br), the thymine adduct **16** (R = Me), and 5,5-dibromobarbituric acid (**17**).[17] Recently we have found that similar reversals occur from monobromo adducts of the type **16** (R = H), as well as those obtained from other oxo- and aminopyrimidines.[2]



15

16



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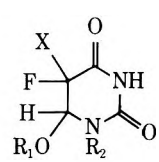


20

Treatment of 6-methyluracil (**11**) with 2 molar equiv of bromine leads to the adduct **14**. The behavior of **14** toward halide ions is similar to that exhibited by **10**, to the extent that it liberates iodine from solutions of potassium iodide, and in the presence of bromide ion and acid it converts **11** to **13**, and is itself converted to **13**.

Table I
Variation of the Rate of Appearance of 5-Bromo-"4,6-dihydroxypyrimidine" (9) with [Br^-] in 1.00 N H_2SO_4[a,b]

[Br^-][c] × 10^4, M	[KBr] × 10^4, M	Total [Br^-] × 10^4, M	k_{obsd} × 10^5, sec^{-1}
2.55		2.55	7.43
2.91		2.91	8.81
3.52		3.52	10.1
5.06		5.06	14.0
5.56		5.56	14.5
5.65		5.65	15.8
5.88		5.88	15.6
6.61		6.61	17.7
6.73		6.73	16.9
8.37		8.37	20.9
8.61		8.61	22.1
10.8		10.8	27.1
11.2		11.2	28.8
12.3		12.3	28.4
16.4		16.4	36.9
5.71	4.91	10.6	26.2
4.83	10.3	15.2	35.2
5.26	13.6	18.9	41.9
4.62	19.7	24.3	54.9
4.87	20.9	25.8	59.3
4.53	27.3	31.8	69.9
4.43	28.3	32.7	67.0

[a] At this acidity, [H_3O^+] = 0.511 M (ref 1). [b] [8] = 1.5×10^{-3} to 6.0×10^{-3} M. [c] Derived from initial bromine concentration.

The reaction of 6-methyluracil (**11**) and "4,6-dihydroxypyrimidine" (**8**) with bromine thus appears to involve rapid formation of the monobromo derivatives, which in turn also react rapidly with bromine to give the corresponding 5,5-dibromopyrimidine derivatives. These subsequently react with substrate to yield the monobromo products. The kinetics of the latter processes were measured spectrophotometrically by monitoring the appearance of 5-bromo products at fixed wavelengths. The initial bromination steps were found to be too fast to be followed by conventional spectrophotometric methods.

Under conditions where the concentrations of **8** and bromine are comparable, complex kinetic behavior is encountered. However, linear first-order plots are obtained when the concentration of **8** exceeds that of bromine by a factor of 4 or more. First-order rate constants obtained in 1.00 N sulfuric acid solutions are independent of substrate concentration, but appear to be linearly dependent on bromine. Since the reaction of **8** with bromine is rapid in comparison to the rate of appearance of **9**, this apparent dependence on bromine may be interpreted as arising from the bromide ion formed in the reaction sequence **8** → **9** → **10**. This was confirmed by experiments in which bromine was added to mixtures of potassium bromide and **8** in solution, where plots of log k_{obsd} *vs.* ([KBr] + initial [Br_2]) yielded the same second-order rate constant (19.8 ± 1.04 M^{-1} sec^{-1}) as that obtained in the absence of potassium bromide (21.6 ± 0.6 M^{-1} sec^{-1}). Kinetic data for these processes are summarized in Table I, those for other acidities being listed in Table II and plotted against bromide ion concentration in Figure 1.

Table II[a]
Variation of the Rate of Appearance of 5-Bromo-"4,6-dihydroxypyrimidine" (9) with $[Br^-]^b$ and $[H_3O^+]$

$[H_2SO_4]$, N	0.100		0.300		0.500		0.700	
$[H_3O^+]$, M	0.059		0.160		0.261		0.361	
$[Br^-] \times 10^4$, M	$k \times 10^3$, sec^{-1}	$[Br^-] \times 10^4$, M	$k \times 10^3$, sec^{-1}	$[Br^-] \times 10^4$, M	$k \times 10^3$, sec^{-1}	$[Br^-] \times 10^4$, M	$k \times 10^3$, sec^{-1}
4.51	2.21	6.25	5.63	3.40	5.30	4.96	8.72
4.84	2.37	7.18	6.60	5.68	7.81	6.16	11.1
5.74	2.52	9.14	7.65	5.96	8.79	8.04	13.5
8.61	3.10	13.7	9.27	6.48	8.35	9.47	15.0
9.19	3.34	13.7	10.4	10.8	13.4	11.8	18.4
11.0	3.63	17.5	11.4	11.4	13.3	15.3	22.7

[a] These data, together with part of that from Table I, are plotted in Figure 1. [b] Derived from initial bromine concentration.

Table III[a]
Variation of the Second-Order Rate Constant k for the Appearance of 5-Bromo-"4,6-dihydroxypyrimidine" (9) with $[H_3O^+]$

$[H_2SO_4]$, N	$[H_3O^+]$, M	k, M^{-1} sec^{-1}
0.100	0.059	2.16
0.300	0.160	5.00
0.500	0.261	10.2
0.700	0.361	13.2
1.00	0.511	21.6
1.00	0.511	19.8[b]

[a] Plotted in Figure 2. [b] Rates were measured in the presence of KBr.

Second-order rate constants which include the bromide ion catalytic coefficient are linearly dependent on acidity. These values are summarized in Table III and plotted in Figure 2. Thus, the conversion of **10** to the 5-bromo derivative **9** seems to be subject to catalysis by bromide ion[18] as well as by hydronium ion.[19] A small contribution from a water reaction or. **10** (R = H) is also suggested by the nonzero intercepts in Figure 1.

Kinetics were also measured for the reaction of the isolable dibromo derivative **10** (R = Me) with **8** in acidic solutions and in the presence of bromide ion, as well as for the reaction of **10** (R = H) (generated by the addition of bromine to the 5-bromo compound **9**) with **8**. In all cases the rate constants obtained were identical within experimental error with those listed in Tables I and II.

These findings may be rationalized by the sequence outlined in Scheme II, and by using the following analysis.[21]

$$8 + Br_2 \xrightarrow[\text{fast}]{k_1} 9 + H^+ + Br^- \quad (1)$$

$$9 + Br_2 \xrightarrow[\text{fast}]{k_2} 10 + H^+ + Br^- \quad (2)$$

$$10 + H^+ + Br^- \xrightarrow[\text{slow}]{k_3} 9 + Br_2 \quad (3)$$

Upon mixing of the substrate **8** and bromine there is rapid formation of both **9** and **10** (eq 1 and 2) and also of bromide ion up to a concentration essentially equal to that of the initial bromine. *Only* after essentially all of the bromine has been consumed by **8** and **9** does the slow back-reaction **10** → **9** (eq 3) become apparent. Moreover, since **8** is in excess, and probably $k_1 > k_2$, any bromine produced by the k_3 step is scavenged by **8** and converted to **9**. That is, during the slow later stages of the reaction, bromine is present only in steady-state amounts. The overall result of the reaction is thus that all of the bromine is converted to **9** (and HBr), since **8** is always in excess.

At any time the rate of formation of **9** is

$$\frac{d[9]}{dt} = (k_1[8] - k_2[9])[Br_2] + k_3[10][H^+][Br^-] \quad (4)$$

and that of bromine is

$$\frac{d[Br_2]}{dt} = k_3[10][H^+][Br^-] - (k_1[8] + k_2[9])[Br_2] \quad (5)$$

During the latter stages of the reaction, bromine is present in steady-state amounts, since both of the processes (eq 1 and 2) which consume bromine are very much faster than that (eq 3) which produces it. Setting eq 5 = 0 gives

$$[Br_2] = \frac{k_3[10][H^+][Br^-]}{k_1[8] + k_2[9]}$$

and substitution into eq 4 yields

$$\frac{d[9]}{dt} = \frac{2k_1k_3[8][10][H^+][Br^-]}{k_1[8] + k_2[9]} \quad (6)$$

Under the conditions of our experiments [8] ≫ [9], and since almost certainly $k_1 > k_2$, eq 6 simplifies to

$$\frac{d[9]}{dt} = 2k_3[10][H^+][Br^-] \quad (7)$$

We believe, therefore, that the slow appearance of **9** which follows an initial rapid increase in absorbance due to **9** arises from the bromide ion induced debromination of **10** *via* **18**. This reaction (eq 3), is, of course, the microscopic reverse of the bromination of **9** (eq 2), and its rate should be dependent upon both acid and bromide ion concentration (eq 7) as observed.

If, during our experiments, **8** were not in excess with respect to initial bromine, the concentration of **9** might exceed that of **8** during the reaction and give rise to a breakdown of the inequality $k_1[8] \gg k_2[9]$. Under these particular circumstances eq 6 would give rise to more complex kinetic behavior, as we have observed.

Similar kinetic behavior was obtained for the reaction of 6-methyluracil with bromine, in that the observed first-order rate constants were linearly dependent on acid strength as well as on bromide ion concentration. However, pseudo-first-order behavior resulted even under conditions where substrate and bromine were of comparable concentrations. Kinetic data for this reaction compare well with those obtained from the reaction of **14** with 6-methyluracil in acidic solutions in the presence of potassium bromide, and imply that **13** is formed from a protonated species such as **19** derived from the dibromo adduct **14**, as illustrated in Scheme I. Rate results are tabulated in Table IV, and the

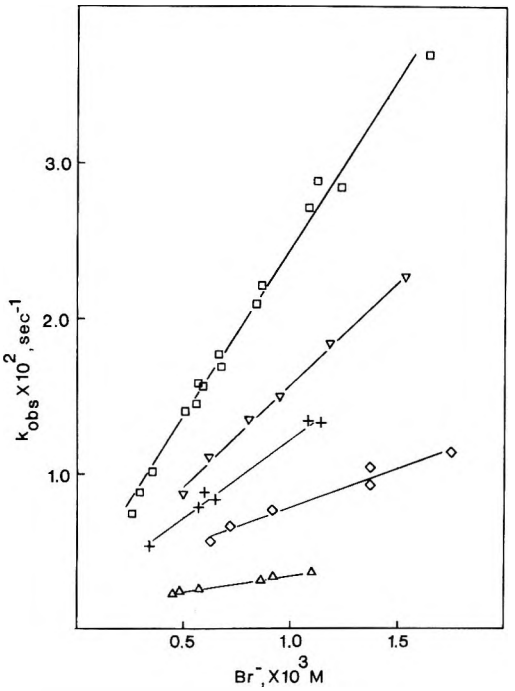


Figure 1. Variation of the rate of appearance of 5-bromo-"4,6-dihydroxypyrimidine" (**9**) with [Br$^-$] in sulfuric acid solutions of the following normalities: □= [*I*] *N*; ▽, 0.700 *N*; +, 0.500 *N*; ◇, 0.300 *N*; △, 0.100 *N*.

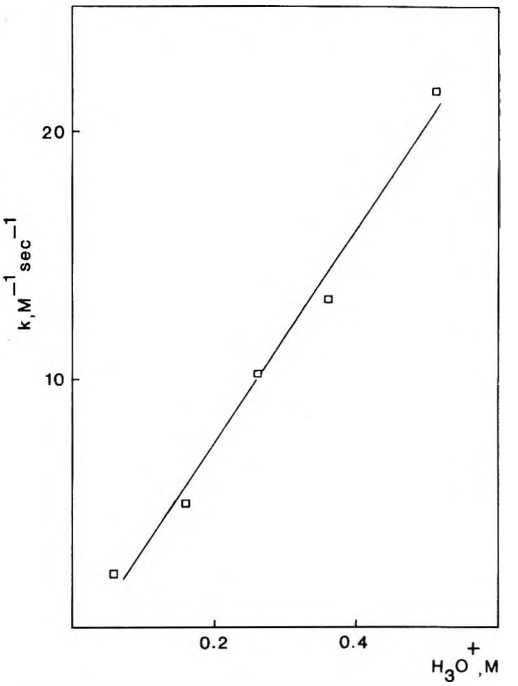


Figure 2. Variation of the second-order rate constant k for the appearance of 5-bromo-"4,6-dihydroxypyrimidine" (**9**) with [H_3O^+].

Table IV
Variation of the Rate of Appearance of 5-Bromo-6-methyluracil (13) with the Acidity Function H_0

[H_2SO_4], *N*	H_0	$k_{obsd}/[Br^-]^a$ × 10^2, M^{-1} sec^{-1}	log ($k_{obsd}/[Br^-]$)
1.00	0.10	0.450	−2.3468
1.20	0.01	0.495[c]	−2.3054
2.00[b]	−0.30	1.53	−1.8163
2.80[b]	−0.55	2.33	−1.6320
3.00	−0.61	2.92[c]	−1.5351
4.00	−0.89	6.33	−1.1984
5.00[b]	−1.16	14.4	−0.8416

[a] Average of two determinations; plotted in Figure 3. [b] Rate data refer to the reaction of **14** with **11** in the presence of KBr. [c] Single determination.

dependence of log (k_{obsd}/[Br$^-$] with the acidity function H_0 is shown in Figure 3.[22]

Analysis of the sequence

$$11 + Br_2 \xrightarrow[\text{fast}]{k_1} 13 + H^+ + Br^-$$

$$13 + Br_2 \xrightarrow[\text{fast}]{k_2} 14 + H^+ + Br^-$$

$$14 + H^+ + Br^- \xrightarrow[\text{slow}]{k_3} 13 + Br_2$$

along the lines outlined for the "4,6-dihydroxypyrimidine"–bromine reaction yields

$$\frac{d[\mathbf{13}]}{dt} = 2k_3[\mathbf{14}][H^+][Br^-] \qquad (8)$$

for the slow appearance of **13** during the latter stages of the reaction of **11** with bromine. The derivation of eq 8 is dependent upon the validity of the inequality $k_1[\mathbf{11}] \gg k_2[\mathbf{13}]$. Since we observe that it is not necessary to have a large excess of 6-methyluracil (**11**) over bromine to obtain good pseudo-first-order kinetics, it would appear that $k_1 \gg k_2$; *i.e.*, the bromination of 6-methyluracil (**11**) is very much faster than that of 5-bromo-6-methyluracil (**13**). The correspondence between our analysis of Scheme I and our experimental observations again leads us to believe that the reaction followed was an acid-catalyzed bromide ion induced debromination, namely **14** → **13**.

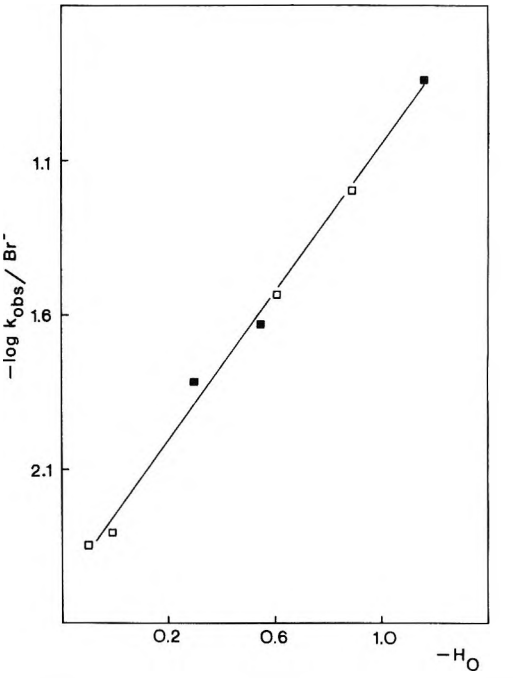
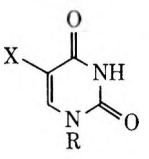


Figure 3. Variation of the rate of appearance of 5-bromo-6-methyluracil (**13**) with the acidity function H_0: □, from the reaction of **11** with bromine; ■, from the reaction of **14** with **11** in the presence of KBr.

Dehalogenation reactions similar to those of **10** and **14** appear to be of significance in biological processes. Dus-

chinsky, *et al.*,[23] have prepared a series of 5,6-substituted 5-fluorodihydrouracils and their corresponding 2′-deoxyribonucleosides **20** (X = Br, Cl; R_1 = H, Me, Et, *t*-Bu, etc; R_2 = H, 2′-deoxyribosyl), and have shown that a qualitative correlation exists between the stability of **20** toward reduced glutathione and its activity against mouse leukemia B82A. Such activity was presumed to arise from the release of 5-fluorouracil or 5-fluorouridine from the dihalogeno adducts **20.** Garrett, *et al.*,[24] have also observed dehalogenation processes in the hydrolysis of 5-iodouridine **21** (X = I; R = 2′-deoxyribosyl). Under acidic conditions, the nucleoside is converted to 5-iodouracil, and deiodination of the latter was postulated to occur *via* an addition–elimination mechanism involving loss of iodonium ion from the adduct **22** (X = I; R = OH). More recently it has been shown that the 5-halouracils **21** (X = Cl, Br, I; R = H) dehalogenate in the presence of sodium bisulfite,[25] and it was suggested that loss of halonium ion occurs from the bisulfite adduct **22** (X = Cl, Br, I; R = OSO_2H).



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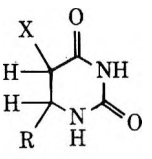

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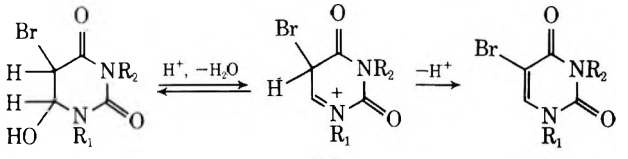
In conclusion we point out the similarities between the debromination reactions of **10** and **14** and the dehydration process **23** → **25.** For the latter, measured isotope effects[2]



23 **24** **25**

R_1 = H, Me; R_2 = H, Me

suggest that the cleavage of the C_5–H bond (**24** → **25**) is rate determining. Therefore, again consistent with the kinetic results presented above, one would expect the breaking of the C_5–Br bonds of **18** (Scheme II) and **19** (Scheme I) to be the rate-determining steps in the conversion of **10** → **9** and **14** → **13,** respectively.

Experimental Section

The melting points given below are uncorrected. Uv measurements were made on a Cary 14 instrument, pmr spectra were obtained from a Varian A-60 spectrometer, and the mass spectrum[26] was run on a Perkin-Elmer Hitachi RMU-6E spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

"4,6-Dihydroxypyrimidine" (8) from Aldrich was recrystallized from water before use.

The following were prepared according to literature methods: **5-bromo-6-methyluracil**[27] **(13)** and **5,5-dibromo-6-hydroxy-6-methyldihydrouracil**[28] **(14).**

5-Bromo-"4,6-dihydroxypyrimidine" (9). This compound has previously been synthesized by the bromination of **8** in acetic acid[14] or warm water,[14] but it may be prepared in higher yield by bromination in methanol.

Bromine (1.6 g, 0.01 mol) in 10 ml of absolute methanol was added to a suspension of "4,6-dihydroxypyrimidine" (**8,** 1.12 g, 0.01 mol) in 10 ml of absolute methanol. Removal of methanol under reduced pressure and recrystallization of the residue from water gave 1.6 g (84%) of **9:** mp 261–263° dec (lit.[14] mp 263–264° dec); pmr (DMSO-d_6) δ 7.82 (broad s, 2), 8.50 (s, 1); uv (1.00 *N* H_2SO_4) λ_{max} (log ϵ) 204 (4.36), 261 (4.05).

5,5-Dibromo-4,6-dioxo-2-methoxyhexahydropyrimidine (10, R = Me). Bromine was added dropwise with stirring to a suspension of **8** (0.56 g, 0.005 mol) in 5 ml of absolute methanol until the color persisted. Refrigeration of the mixture and filtration afforded a pale yellow material which was found to contain some of the starting material **8.** The bromination process was repeated to give 1.23 g (82%) of the dibromo derivative **10** (R = Me) as white crystals which were recrystallized from acetone–ligroin (bp 30–60°). The compound melted at 176–178° with strong effervescence, resolidified to a yellow material which darkened above 220°, and melted with decomposition at 232–240°: pmr (DMSO-d_6) δ 3.23 (s, 3), 5.47 (t, 1), 9.76 (d, 2) (J = 3.1 Hz). Addition of D_2O led to the collapse of the low-field signals to a singlet. The mass spectrum (run at a source temperature of 170°)[26] did not show a molecular ion peak corresponding to *m/e* 302, but showed triplets of intensity ratio 1:2:1 at *m/e* 273, 271, and 269 and at 272, 270, and 268.

Anal. Calcd for $C_5H_6N_2O_3Br_2$: C, 19.89; H, 2.00; N, 9.28; Br, 52.93. Found: C, 19.97; H, 1.90; N, 9.29; Br, 52.92.

Kinetic Procedures. Sulfuric acid and sodium thiosulfate were prepared from commercial standard volumetric concentrates. Solutions of bromine in aqueous sulfuric acid were estimated by titration against sodium thiosulfate. The concentration of hydronium ion in dilute sulfuric acid was calculated as described earlier.[1] For solutions of stronger acidity, "weight per cent H_2SO_4" was converted to normality using appropriate density values,[29] and corresponding H_0 values for the latter[30] were fitted to a power series, which then allowed direct conversion of normality to H_0 for any value of normality.

Rates of product formation were measured by monitoring a suitable wavelength in the 300–340-nm region using a Cary 14 spectrophotometer. Temperature control was maintained by circulating water through the cell holders from a Neslab TE9 constant-temperature bath kept at 30.00 ± 0.02°. Solutions of substrate were pipetted directly into the cell, and the reaction was started after temperature equilibration by adding 0.1 or 0.2 ml of the reactant solution. Measurements were normally taken over at least 3 half-lives for the faster runs $t_{1/2} \leq 20$ min) and 2 half-lives for the slower runs. The rate constants reported were obtained from first-order rate plots whose correlation coefficients exceeded 0.9998 for the slower and 0.9996 for the faster runs.

Acknowledgment. The authors thank the National Research Council of Canada for financial support.

Registry No.—**8a,** 1193-24-4; **8b,** 25286-58-2; **9a,** 15726-38-2; **9b,** 52176-13-3; **10** (R = Me), 52176-14-4; **13,** 15018-56-1.

References and Notes

(1) O. S. Tee and S. Banerjee, *J. Chem. Soc., Chem. Commun.,* 1032 (1972); *Can. J. Chem.,* **52,** 451 (1974).
(2) O. S. Tee and S. Banerjee, *J. Chem. Soc., Chem. Commun.,* 535 (1974), and unpublished results.
(3) A. M. Moore and S. M. Anderson, *Can. J. Chem.,* **37,** 590 (1959).
(4) S. Y. Wang, *J. Org. Chem.,* **24,** 11 (1959).
(5) The kinetics of the dehydration reaction **12** → **13** have been studied.[2]
(6) Studies into the structure of this compound have been reviewed by M. Prystas, *Collect. Czech. Chem. Commun.,* **32,** 4241 (1967).
(7) Y. Inoue, N. Furutachi, and K. Nakanishi, *J. Org. Chem.,* **31,** 175 (1966).
(8) G. M. Kheifets, N. V. Khromov-Borisov, and A. I. Kol'tsov, *Dokl. Akad. Nauk SSSR,* **166,** 635 (1966).
(9) A. R. Katritzky, M. Kingsland, and O. S. Tee, *Chem. Commun.,* 289 (1968); *J. Chem. Soc. B,* 1226 (1968).
(10) O. S. Tee, Ph.D. Thesis, University of East Anglia, 1967.
(11) The choice of an acidic medium was made for three reasons: (a) to swamp out any effects of HBr produced during substitution; (b) to facilitate interconversion of the tautomers **8a** and **8b;** (c) for the comparison of results to our previous studies.[1,2]
(12) D. J. Brown and T. Teitei, *Aust. J. Chem.,* **17,** 567 (1964).
(13) J. R. Marshall and J. Walker, *J. Chem. Soc.,* 1004 (1951).
(14) J. Chesterfield, J. F. W. McOmie, and E. R. Sayer *J. Chem. Soc.,* 3478 (1955).
(15) Ring opening could lead to dibromomalonic acid, which readily decarboxylates.[16]
(16) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. I, Elsevier, Amsterdam, 1952, Part B.
(17) D. J. Brown, "The Pyrimidines," Vol. XVI, "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1962.
(18) The presence of potassium chloride had no effect on the reaction rate.
(19) Iodide-induced dehalogenation of vicinal dibromides in polar solvents is well known.[20]
(20) A. F. Cockerill in "Comprehensive Chemical Kinetics," Vol. IX, C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, Amsterdam, 1973.
(21) An equivalent analysis pertains to Scheme I.
(22) A water reaction on **14** would tend to deviate the plot toward nonlinearity. However, the magnitude of this reaction is likely to be small and is ignored.
(23) R. Duschinsky, T. Gabriel, W. Tautz, A. Nussbaum, M. Hoffer, E. Grunberg, J. H. Burchenal, and J. J. Fox, *J. Med. Chem.,* **10,** 47 (1967).

(24) E. R. Garrett, T. Suzuki, and D. J. Weber, *J. Amer. Chem. Soc.*, **86**, 4460 (1964).
(25) E. G. Sander and C. L. Deyrup, *Arch. Biochem. Biophys.*, **150**, 600 (1972).
(26) We thank Dr. R. T. B. Rye for taking the mass spectrum.
(27) R. C. Elderfield and R. N. Prasad, *J. Org. Chem.*, **25**, 1583 (1960).
(28) R. Behrend, *Justus Liebigs Ann. Chem.*, **229**, 18 (1885).
(29) "International Critical Tables," **3**, 56 (1928).
(30) C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, **91**, 6654 (1969).

Three-Membered Rings. VII. Solvent Control of the Cis–Trans Isomer Ratio in the Preparation of a Phosphonate Substituted Cyclopropane[1]

Eckhard W. Hellmuth, John A. Kaczynski, James Low, and Layton L. McCoy*

Department of Chemistry, University of Missouri—Kansas City, Kansas City, Missouri 64110

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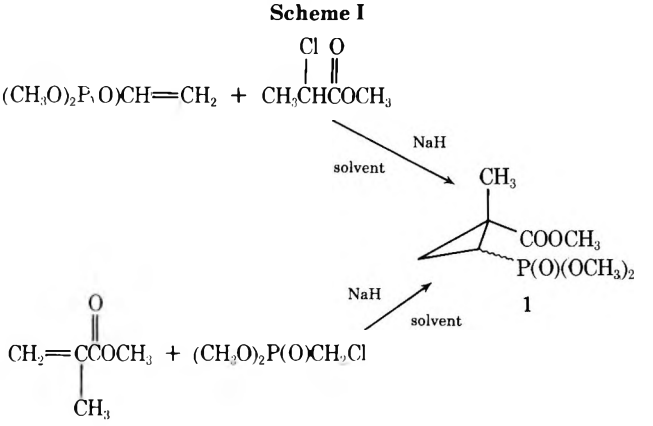
Dimethyl 2-methyl-2-carbomethoxycyclopropylphosphonate was prepared by the reaction of methyl methacrylate with dimethyl chloromethylphosphonate and sodium hydride in solvent mixtures varying from pure benzene through benzene–dimethylformamide to pure dimethylformamide. Two isomers were observed in all solvents. The stereochemistry proposed for them is based on analysis of their nuclear magnetic resonance spectra. The ratio of trans isomer to cis isomer was determined by gas chromatographic analysis and confirmed by nuclear magnetic resonance spectral analysis. Although log (trans isomer/cis isomer) produces a linear relationship when plotted against the Kirkwood–Onsager term, $(\epsilon - 1)/(2\epsilon + 1)$, for solvent polarity, the correlation is the inverse of nearly all such cases previously reported, *i.e.*, the cis isomer predominates in the polar solvent dimethylformamide and the trans isomer predominates in the nonpolar solvent benzene.

A general procedure for the preparation of polysubstituted cyclopropanes has been examined in earlier papers of this series[2] and in work reported by others.[3] The procedure involves treatment of an α-halo compound with an α,β-unsaturated compound in the presence of a base and solvent. All of the groups reported to "activate" the α-halogen compound and the olefinic compound might be termed carbon functional groups, *i.e.*, functional groups with a central carbon such as esters, amides, nitriles, and ketones. Cyclopropane products thus formed are at least difunctional. The functional groups, the "activating" groups, are on adjacent positions of the cyclopropane ring, oriented cis or trans. It has been observed that the cis/trans isomer ratio is dependent on the solvent: when the solvent is nonpolar, *e.g.*, benzene, the cis isomer predominates, while when the solvent is polar, *e.g.*, dimethylformamide, the cis/trans isomer ratio decreases, usually leading to a preponderance of the trans isomer.[2b] The present report gives an extension of the previous work to include a heteroatom functional group, the phosphonate moiety, and an examination of the solvent effect in this system.

The dimethyl phosphonate group was used to activate either the α-halo group or the olefinic group as shown in Scheme I.[4] Although a variety of conditions for the preparation of compound 1 were used, no systematic study to optimize the yield was attempted. Gas chromatographic analysis showed the presence of two isomers as expected. Complete separation of these isomers was not accomplished in either analytical or preparative scale gas chromatography, but separation was sufficient to determine isomer ratios (confirmed by integrated peak ratios in the nmr spectra of mixtures), to obtain the nmr spectra of each isomer, and to give enriched materials for subsequent saponification. The first isomer eluted in these separations is designated as isomer A, the second isomer B. Control experiments showed that these isomers do not interconvert under the preparative reaction conditions.

Scheme I



Preparation of compound 1 in solvents varying from *N,N*-dimethylformamide (DMF) through mixtures of DMF with benzene to benzene produced changes in the ratio isomer B/isomer A, as seen in Table I. Although these studies of the effect of solvent used the dimethyl chloromethylphosphonate pathway, the dimethyl vinylphosphonate pathway did show the same isomer preference in the nonpolar solvent benzene (the polar solvent dimethylformamide was not examined). In similar studies of isomer ratio–solvent relationships in the preparation of some cyclopro-

Table I
Solvent Composition, Kirkwood–Onsager Term Values, Yields, and Isomer Ratios for the Preparation of Dimethyl 2-Methyl-2-carbomethoxycyclopropylphosphonate

Solvent ratio $HC(=O)NMe_2$:C_6H_6	$(\epsilon - 1)/(2\epsilon + 1)$	Yield of phosphonate, %	B/A (trans/cis)	Log (trans/cis)
10:0	0.4803	18	0.19	−0.72
9:1	0.4631	19	0.23	−0.64
8:2	0.4446	38	0.27	−0.57
7:3	0.4246	37	0.42	−0.38
6:4	0.4034	26	0.56	−0.25
5:5	0.3803	35	0.87	−0.06
4:6	0.3555	12	1.27	+0.10
3:7	0.3284	16	1.75	+0.24
2:8	0.2984	8	2.9	+0.46
1:9	0.2627	17	7.9	+0.90
0:10	0.2302	6	14.8	+1.17

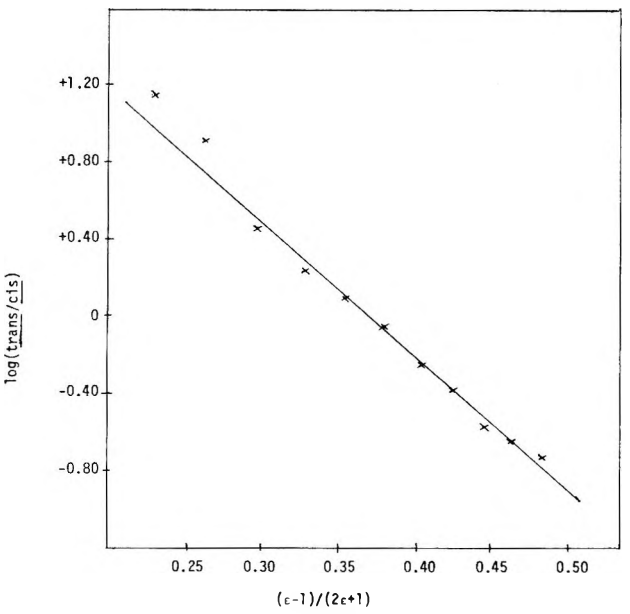


Figure 1. Correlation of isomer ratio [log (trans/cis)] with solvent polarity $[(\epsilon - 1)/(2\epsilon + 1)]$ in the preparation of dimethyl 2-methyl-2-carbomethoxycyclopropylphosphonate.

panedicarboxylic esters, Inouye[5,6] showed that such relationships were consistent with the Kirkwood theory for the effect of the dielectric constant of the media on the reaction rate.[7] Thus, a plot of log (isomer B/isomer A) against the function $(\epsilon - 1)/(2\epsilon + 1)$ where ϵ is the dielectric constant of solvent gives the result seen in Figure 1.

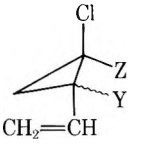
The proposed stereochemistry of the two isomers is based primarily on nmr studies. There are only minor differences in chemical shifts and coupling of the ring hydrogens and the carbomethoxy hydrogens of the two isomers. However, the *C*-methyl hydrogens and the phosphorus methoxy hydrogens in the two isomers are quite different. In isomer A, the *C*-methyl hydrogens appear as a singlet (δ 1.50) while in isomer B they appear as a doublet (δ 1.38, J_{P-H} = 2.3 Hz). On the basis of work by several groups[8] it appears that P–H coupling through two (or three) carbon atoms varies with the dihedral angle as in the Karplus relationship.[9] In the two possible isomers, the C–C–methyl and C–C–phosphorus dihedral angles were estimated at 0 and 105° from models. The largest coupling would occur at 0° and this would be expected to produce an observable doublet. Thus, in isomer B the *C*-methyl would be cis to the phosphonate group or on the basis of the previous discussion would be called the trans isomer (phosphonate and carbomethoxy groups trans). This assignment is consistent with the upfield shift of the doublet arising from through-space shielding of the methyl group by the phosphonate group cis to it.[10] In a somewhat different way, the P *O*-methyl hydrogens confirm this assignment. For isomer A these hydrogens appear as two sets of doublets (δ 3.72, J_{P-H} = 11.2 Hz; δ 3.73, J_{P-H} = 11.0 Hz) while in isomer B they occur as one doublet (δ 3.67, J_{P-H} = 11.2 Hz). P–H coupling will result in the doublets observed, while the appearance of two sets of doublets might be diastereotopic or due to restricted rotation of the phosphonate group. Models suggest that a cis arrangement of the two functional groups produces very severe crowding and possible hindrance to rotation of the phosphonate group; a trans arrangement leaves the phosphonate group much less restricted. Examination of the nmr spectra of isomer A at elevated temperatures (up to 180°) showed no change in the set of doublets, but examination of isomer B at low temperature (down to −70°) changes its nmr spectrum to give a set of doublets very similar to those observed for isomer A. This is consistent with the idea of hindered rotation for the phosphonate group, and the cis relationship of the two bulky functional groups in isomer A.[11]

Saponification of isomer B produced a triacid in which the *C*-methyl produces a doublet (δ 1.40, J_{P-H} = 1.8 Hz) in its nmr spectra. Saponification of isomer A was more difficult and a pure acid was not obtained. However, the nmr spectrum (in D_2O) of the crude acid isolated showed the C-methyl singlet at δ 1.47 and that one phosphonate methyl group (δ 3.70, d, J_{P-H} = 11 Hz) was still present, *i.e.*, unsaponified, possibly owing to the marked steric hindrance and charge concentration with the two functional groups oriented cis.

Thus, we propose that isomer A is the cis isomer and isomer B is the trans isomer. This leads to the interesting observation (Figure 1, Table I) that the effect of solvent on isomer formation apparently is the reverse of that observed previously,[2,3,5,6] *i.e.*, the cis isomer predominates in the polar solvent while the trans isomer predominates in the nonpolar solvent. Although unexpected, this result is not surprising. Application of the Kirkwood theory of solvent effects on reaction rates to the reactions studied here leads to the equation

$$\ln k_t/k_c = C_0 - 1/kT \cdot (\epsilon - 1)/(2\epsilon + 1) \cdot (\mu_c^{*2}/r_c^{*3} - \mu_t^{*2}/r_t^{*3})$$

where C_0, k, and T are constants for the present discussion, μ_i^* is the dipole for the transition state of the i reaction, r_i^* is the radius of the same transition state, and ϵ is the dielectric constant for the solvent. Clearly, the slope of the line produced by plotting $\ln K_t/k_c$ *vs.* $(\epsilon - 1)/(2\epsilon + 1)$ is determined by the relative dipoles and sizes of the transition states for the cis and trans reactions. Values for these dipoles and sizes can be estimated so as to rationalize observed results,[5] but it is unlikely that sufficiently precise values can be determined *a priori* so as to give reliable predictions. Nearly all previous studies have involved "nonactivating" substituents, *i.e.*, substituents other than the ester, nitrile, or keto functions defining the stereochemistry, which are alkyl groups, and in these cases the generalization of nonpolar solvent–cis isomer, polar solvent–trans isomer is consistent. However, it should be noted that when chlorine is one of the "nonactivating" substituents, although the solvent–isomer ratio trend is still present, the cis isomer predominates in *both* polar and nonpolar solvents.[2b] Further, more recently and subsequent to the completion of this work, Ducher, Sudre, and Vessiere[12] have reported a similar inversion of the solvent–isomer ratio relation. Thus for



with Y = $COOCH_3$ and Z = $COOCH_3$ or CN, only the cis isomer is formed independant of the solvent used ($PhCH_3$ or $[(CH_3)_2N]_3PO$) and with Y = CN the per cent of cis isomer in the isolated product is as follows,

	Z = $COOCH_3$	Z = CN
$PhCH_3$	35	30
$[(CH_3)_2N]_3PO$	62	74

i.e., the cis isomer predominates in the more polar solvent. Thus, the solvent polarity–isomer ratio relation established for systems having alkyl substituents and ester or nitrile activating groups appears not necessarily to be applicable

with other types of polar substituents and activating groups. The present work is consistent with and supports the general concept of stereochemical control by transition state dipole–solvent polarity interaction proposed by Inouye.[5] However, in terms of the expression derived from the Kirkwood theory, it is not possible in the general case to make valid, reliable *predictions* as to the nature of the solvent–isomer ratio relation, *i.e.*, which isomer will predominate in which type of solvent, or even if there will be a change in isomer in going from one solvent to another.

Experimental Section

General. Nuclear magnetic resonance spectra were taken on a Varian T-60 spectrometer, or a JEOL JNM-4H-100 spectrometer; the esters were observed in carbon tetrachloride solution and the acids in D_2O unless otherwise mentioned. Gas–liquid chromatographic analyses were carried out on a Varian Aerograph A-90-P gas chromatograph.[13]

Preparation of Dimethyl 2-Methyl-2-carbomethoxycyclopropylphosphonate. A. Dimethyl Chloromethylphosphonate.[14] The general conditions are essentially those of Inouye, *et al.*[6] Pertinent results are shown in Table I.

B. Dimethyl Vinylphosphonate.[15] General procedure A[2b] modified so as to filter out the sodium chloride rather than wash it out with water was used; a 57% yield of cyclopropane ester mixture was obtained (bp 122–129°, 1.8 mm).

Products from runs in solvent ratios of 5:5, 4:6, and 3:7 (Table I) were combined and distilled (bp 85–86°, 0.4–0.5 mm). Chromatographic analysis showed only the two isomer peaks in the ratio 51% trans, 49% cis (nmr analysis showed 49% trans). The sample was analyzed. *Anal.* Calcd. for $C_8H_{15}PO_5$: C; 43.25; H, 6.81; P, 13.94. Found: C, 43.13; H, 7.30; P, 13.59.

Saponification of Dimethyl 2-Methyl-2-carbomethoxycyclopropylphosphonate. A. Saponification of an ester mixture containing a preponderance (90%) of trans ester occurred readily with aqueous methanolic sodium hydroxide upon slight warming. Concentration of the solution and then addition of concentrated hydrochloric acid precipitated most of the sodium chloride, which was removed. Concentration of the acid solution, solution of the concentrate in acetonitrile, and storage in a refrigerator produced a crystalline acid after a few days. Recrystallization from acetic acid containing a few drops of acetic anhydride resulted in the trans triacid, mp 159.5–160.5°. *Anal.* Calcd for $C_5H_9O_5P$: C, 33.35; H, 5.04; P, 17.20. Found: C, 33.24; H, 4.92; P, 17.12. The mother liquors from the trans triacid produced no further crystalline material. However, both the trans triacid and the mother liquors on treatment with diazomethane produced the triesters, the trans triacid giving pure trans triester and the mother liquors giving a mixture of triesters containing about 75% cis isomer.

B. Triester (76% cis) was saponified under the same conditions. A crystalline acid, mp 120–124°, was isolated; although a variety of solvents were used, the melting point could not be narrowed. An nmr spectrum of this material in dimethyl sulfoxide showed acidic protons at δ 8.43, with the area of this peak being two-thirds the area of the P(O)(OCH_3) doublet (δ 3.55) or the ring methyl group singlet (δ 1.35).

Isomerization Control Experiments. A sample of the triester (65% cis) treated with sodium hydride for 74 hr at temperatures ranging from 25 to 85° showed no change in isomer ratio. Similarly, another sample (50% cis) refluxed with sodium methoxide in methanol for 48 hr showed no change in isomer composition. In several preparations of the triester, samples were removed while reaction was occurring; in all cases, the isomer ratios were essentially the same at all stages of reaction.

Nmr Temperature Studies. These studies were carried out with the JEOL instrument. The low-temperature studies (trans isomer) were carried out in $(CD_3)_2CO$ (15% v/v) with 1–5% tetramethylsilane added as an internal reference. The sample was cooled slowly by cold nitrogen vapor; below −80° the mixture became too viscous for study. Dimethyl sulfoxide was used for the high temperature, the solvent protons acting as reference (δ 2.5). The mixture was heated slowly to the boiling point (189°). For both the hot and cold studies, spectra were taken at room temperature and several intermediate temperatures.

Registry No.—*cis*-**1**, 52176-07-05; *trans*-**1**, 52176-08-6; *trans*-**1** triacid, 52176-09-7; dimethyl vinylphosphonate, 4645-32-3; dimethyl chloromethylphosphonate, 6346-15-2; methyl 2-chloropropanoate, 17639-93-9; methyl methacrylate, 80-62-6.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of John A. Kaczynski, Jr., University of Missouri—Kansas City, 1974, and the M.S. Thesis of James Low, University of Missouri—Kansas City, 1970.

(2) (a) L. L. McCoy, *J. Org. Chem.*, **25**, 2078 (1960); (b) L. L. McCoy, *J. Amer. Chem. Soc.*, **84**, 2246 (1962); (c) L. L. McCoy and G. W. Nachtigall, *J. Org. Chem.*, **27**, 4312 (1962).

(3) See footnote 1 of ref 2b for an extensive but not exhaustive list of such papers.

(4) The obvious combination of the α-halo and olefinic phosphonate compounds with base and solvent to give a diphosphonate substituted cyclopropane has been tried. Although a diphosphonate apparently is formed, we have been unable to purify and characterize it.

(5) Y. Inouye, S. Inamasu, M. Horiike, M. Ohno, and H. M. Walborsky, *Tetrahedron*, **24**, 2907 (1968).

(6) S. Inamasu, M. Horiike, and Y. Inouye, *Bull. Chem. Soc. Jap.*, **42**, 1393 (1969).

(7) J. G. Kirkwood, *J. Chem. Phys.*, **2**, 351 (1934).

(8) (a) C. Benezra, *Tetrahedron Lett.*, 4471 (1969); (b) C. Benezra, *J. Amer. Chem. Soc.*, **95**, 6890 (1973); (c) J. A. Ross and M. D. Martz, *J. Org. Chem.*, **34**, 399 (1969); (d) D. Seyferth, R. S. Marmor, and P. Hilbert, *ibid.*, **36**, 1379 (1971).

(9) M. Karpulus, *J. Chem. Phys.*, **30**, 11 (1959).

(10) L. M. Jackman and S. Sternhell, "Applicatfons of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 88.

(11) There do not seem to be any clear-cut examples of hindered rotation of phosphonate groups reported. However, possible examples are found: (a) D. Seyferth, R. S. Marmor, and P. Hilbert, *J. Org. Chem.*, **36**, 1379 (1971); (b) C. Benezra and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2270 (1961).

(12) S. Ducher, J. P. Suncre, and R. Vessiere, *C. R. Acad. Sci., Ser. C*, 537 (1974).

(13) A variety of columns and conditions were examined; most gave no or unsatisfactory separation. In some of the early work Apiezon L was used, but for the work reported here, phenyl diethanolamine succinate was used. It should be noted that the order of elution of the two isomers is reversed with these two column materials.

(14) M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 634 (1950).

(15) Prepared by reaction of 1,2-dibromethane and triethyl phosphite [G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **70**, 1971 (1948)] followed by treatment with phosphorus pentachloride and conversion of the resulting phosphonic dichloride to the dimethyl ester.

Micellar Effects on the Acid-Catalyzed Decomposition of Monoalkyl Xanthates[1]

Clifford A. Bunton,* Juan E. Salame, and Luis Sepulveda

Department of Chemistry, University of California, Santa Barbara, California 93106, and Faculty of Chemical Sciences, University of Chile, Santiago, Chile

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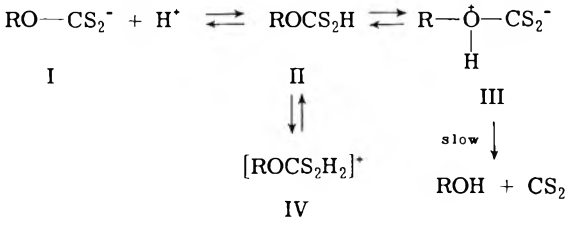
At pH >2 the decomposition of ethyl, *n*-butyl, and *n*-octyl xanthate ion to the alcohol and CS_2 is inhibited by cationic micelles of cetyltrimethylammonium bromide (CTABr) and catalyzed by anionic micelles of sodium lauryl sulfate (NaLS) and nonionic micelles of Triton X-100. These effects can be rationalized in terms of micellar effects upon the protonation of the xanthate ion, and this rationalization is supported by micellar effects upon the apparent dissociation constants of the alkylxanthic acids. At low pH CTABr catalyzes the reaction in part because it decreases protonation of the xanthic acid to its unreactive conjugate acid; whereas under these conditions NaLS inhibits reaction, but the nonionic surfactant Brij 58 has no effect.

Monoalkyl xanthates (I) are rapidly hydrolyzed in dilute acid,[2] and the rate-limiting step is a spontaneous heterolysis of the undissociated acid (II).[4-6] The zwitterion (III) may be an intermediate formed in low concentration, or a proton transfer from sulfur to oxygen could be concerted with C–O bond breaking.



The protonated ester (IV) is formed at low pH and is unreactive, unless the group R can be eliminated readily as a carbocation.[6]

The use of monoalkyl xanthates in ore flotation and cellulose processing stimulated work on their hydrolysis under homogeneous conditions,[3-6] but it seemed that synthetic surfactants might provide useful models for hydrolysis under industrial conditions because reaction in the presence of micellized surfactants could mimic that in the presence of colloids or larger sized particles. In addition alkylxanthate hydrolysis is often an undesired reaction which wastes material, so that its micellar inhibition could be useful.[7]

Experimental Section

Materials. The monoalkyl xanthates were commercial samples or were prepared, as the potassium salts, by standard methods.[3-5,11] The ionic surfactants, cetyltrimethylammonium bromide ($C_{16}H_{33}NMe_3Br$, CTABr) and sodium lauryl sulfate ($C_{12}H_{25}OSO_3Na$, NaLS), were purified by repeated recrystallizations, and the nonionic surfactants, Triton X-100 and Brij 58 (polyoxyethylene-20-cetyl ether) were used without further purification. Deionized and redistilled water was used to prepare the solutions.

Kinetics. The reaction was followed spectrophotometrically at 25.0° using methods already described.[6] The reactions at low pH, where the substrate is present as the xanthic acid, were followed at 270 nm, and Triton, which absorbs at this wavelength, could not be used under these conditions, so Brij was then used as a nonionic surfactant. Reaction at high pH was followed at 301 nm. Acetate buffer (0.02 *M*) was generally used to control the pH, and dilute HCl was used at low pH.

The products were the alcohol and CS_2, as in the absence of surfactants,[3-6] and trace metal effects were unimportant, as shown by the absence of any effect by added EDTA. The pH of the reaction solutions was measured in the presence of the surfactants. The observed first-order rate constants, k_ψ, are in reciprocal seconds, and the concentration of surfactant (detergent) is denoted as C_D.

The decompositions of ethyl and *n*-butyl xanthate have been examined over a wide pH range in the absence of surfactants.[4-6] The results for *n*-octyl xanthate show that its decomposition follows a pattern similar to that of the other alkyl xanthates. A plot of log k_ψ against pH has a slope of −1, and the rate levels off at low pH (Table I) for reaction in the absence of added surfactant.

Table I
Effect of pH on the Hydrolysis of *n*-Octyl Xanthate[a]

$10^3\ C_{HCl}$, *M*	pH[b]	$10^3\ k_\psi$, sec^{-1}	log k_ψ − log C_H[+c]
	5.40	0.016	0.60
	4.50	0.11	0.53
	3.55	0.94	0.32
1.0		3.33	0.52
2.0		6.13	0.49
3.1		9.50	0.44
5.0		16.6	0.51
10.0		26.0	0.42
20.0		35.9	0.26
50.0		54.7	0.05

[a] In dilute HCl at 25.0° except where specified. [b] In buffer. [c] Log k_ψ + pH for reactions done in buffered solutions.

Determination of Apparent Dissociation Constant. The absorbance at 301 nm of a solution of *n*-butyl xanthate at various pH in water or the appropriate surfactant was determined at various times, the absorbances were extrapolated back to the time of mixing, and the absorbances of an equimolar solution of *n*-butyl xanthate were measured under the same conditions. These experiments were repeated in solutions of various pH. The apparent dissociation constant "K_a" was calculated using eq 1, where A and A_x

$$\frac{A_x}{\epsilon_x(A_x - A)} = \frac{K_a}{a_H + \alpha} + \frac{1}{\alpha} \qquad (1)$$

are respectively the absorbances at a chosen pH and in alkaline solution, ϵ_x is the extinction coefficient of *n*-butyl xanthate in the surfactant solution, α is the difference between the extinction coefficients of xanthate ion and xanthic acid, and $a_{H^+} \equiv -\log$ pH in the presence of surfactant. The pH range for these experiments was 1.5–2.8, and the value of α for all the experiments was approximately 16,500.

Results and Discussion

Micelles could change the reaction rate in several ways: by affecting (1) conversion of xanthate ion (I) into the reactive xanthic acid (II), or (2) protonation of xanthic acid (II), giving the unreactive conjugate acid (IV), and (3) the rate of decomposition of xanthic acid (II) to products.

The simplest approach to this problem was to examine the micellar effects either at low pH (<1) where xanthate ion is absent or at higher pH (~3) where xanthic acid is fully ionized.[12] We also measured the apparent values of pK_a, and as expected we found that the acid dissociation of

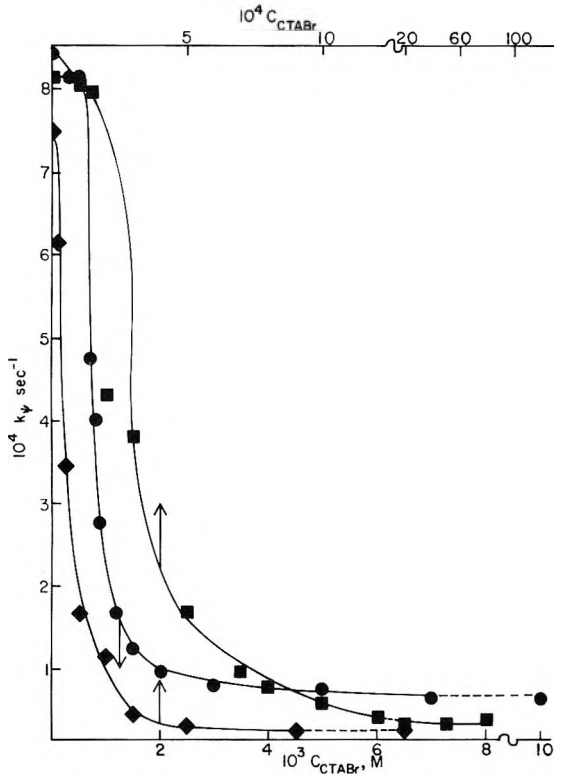


Figure 1. Effect of cationic micelles on the decomposition of *n*-alkyl xanthates at pH 3.65: ●, Et; ■, *n*-Bu; ♦, *n*-octyl.

xanthic acid was increased by CTABr and decreased by Triton X-100 and NaLS; and these effects seem to be of key importance in determining the effects on reaction rate at pH > 3. Under all conditions the effects of micellized surfactants increase with increasing length of the *n*-alkyl group of the xanthate, as is generally found for micellar catalysis and inhibition.[8-10]

(1) At high pH where xanthate ion (I) is the bulk species, anionic micelles should increase the amount of reactive xanthic acid (II) present, and cationic micelles should have the opposite effect. (2) At low pH cationic micelles should decrease protonation of the reactive xanthic acid (II) which gives the unreactive conjugate acid (IV), and anionic micelles should have the opposite effect. (3) If we accept that the transition state is akin to the zwitterion (III) we would expect that incorporation of the substrate deeply into the micelle might hinder decomposition of the reactive xanthic acid by making it difficult for water molecules to hydrogen bond to the hydroxyl group of III, or to transfer a proton from sulfur to oxygen. However, there might be offsetting Coulombic interactions between the ionic head groups of the micelle and the anionic sulfur atoms, and evidence from reaction at pH 0 suggests that the decomposition step is slightly assisted by CTABr and hindered by NaLS.

Reaction at pH > 3. At this pH the xanthate ion is the bulk species, and because anionic micelles increase and cationic micelles decrease the reaction rate (Table II and Figure 1) their most important effect is to change the protonation equilibrium I ⇄ II, and effects on the rate of decomposition of alkylxanthic acid (II) seem to be less important.

The results at any given pH[13] are relatively simple. Cationic micelles of CTABr inhibit the reactions both in acetate buffer (Figure 1) and in 10^{-3} *M* HCl (Table III). The micellar inhibition increases sharply with increasing length of the *n*-alkyl group of the xanthate (Figure 1). The concentration of CTABr ($C_{1/2}$) required to halve the reaction rate (Table IV) gives an approximate indication of the strength of substrate–micelle bonding and shows the importance of the hydrophobic *n*-alkyl group. Because the relation between rate constant and surfactant concentration depends on pH, these values in Table IV apply only at the pH specified.

Table II
Rate Enhancement by NaLS[a]

$10^3 C_{NaLS}$, *M*	Alkyl group: Et	*n*-Bu	*n*-Octyl
	7.7	7.1	6.8
1		7.93	7.20
5	7.16	8.73	32.2
10	7.75	10.1	73.5
15		12.6	
20	7.65	14.0	
25		15.7	120
50	7.34	23.6	130
75	8.86		123
100	11.9	30.6	129
400		58	

[a] Values of $10^4 k_\psi$, sec^{-1}, at 25.0° and pH 3.7.

Table III
Effect of CTABr on the Hydrolysis of *n*-Butyl Xanthate[a]

$10^3 C_D$, *M*	$10^3 k_\psi$, sec^{-1}	$10^3 C_D$, *M*	$10^3 k_\psi$, sec^{-1}
	3.69	8.0	1.51
1.0	3.61	16.0	0.35
3.0	3.02	30.0	0.16
		60.0	0.17

[a] In 10^{-3} *M* HCl.

Table IV
Surfactant Concentrations for Half Rate Enhancement or Inhibition[a]

Alkyl xanthate	Surfactant: CTABr[b]	NaLS[c]	Triton[c]
Et	8×10^{-4}		
n-Bu	3×10^{-4}	~0.1	5×10^{-3}
n-Octyl	4×10^{-5}	8×10^{-3}	1.3×10^{-3}

[a] Molarity of surfactant for 50% effect. [b] At pH 3.65. [c] At pH 3.7.

Anionic micelles of NaLS and nonionic micelles of Triton catalyze the decomposition of *n*-alkyl xanthates at pH > 3 (Tables II and V). The catalysis increases, as expected, with increasing length of the *n*-alkyl group of the xanthate, and the concentration of surfactant needed for half rate enhancement similarly decreases (Table IV). The values of $C_{1/2}$ for *n*-butyl xanthate are approximate because we would have to go to very high surfactant concentrations to obtain rate plateaux.

Inhibition is observed with very low concentrations of CTABr, but much higher concentrations of NaLS are needed for rate enhancement, showing that the strongest interactions are between cationic micelles and alkyl xanthate ion (I).

Triton is as effective as NaLS in speeding the reaction (Tables II and V), and its nonionic micelles are effective in low concentration, showing the importance of hydrophobic as compared with Coulombic interactions.

The approximate maximum observed rate enhancements in micelles of NaLS at pH 3.7 follow: Et, 1.5-fold; *n*-Bu, 8-fold; *n*-octyl, 19-fold. With Triton they follow: Et, 2.5-fold; *n*-Bu, 7-fold; *n*-octyl, 16-fold (Tables II and V). However, it should be noted that these rate enhancements apply only

Table V
Rate Enhancement by Triton[a]

10^3 C_{Triton}, M	Alkyl group: Et	n-Bu	n-Octyl
	7.7	7.1	6.8
0.2	7.98	7.99	12.1
0.5	8.49	8.66	26.9
1.0	9.29	10.1	49.4
2.0	9.60	13.3	78.9
4.0	11.4	19.3	101
6.0	16.3	34.2	108
8.0	19.3	47.2	111
10.0	19.5	50.8	110

[a] Values of 10^4 k_ψ, sec^{-1}, at 25.0° and pH 3.7.

Table VI
Effect of pH on the Hydrolysis of *n*-Octyl Xanthate in NaLS[a]

10^3 C_{NaLS}, M	Medium: 10^{-3} M HCl	pH 2.9	pH 3.3
	33.0	45.7	18.4
1	33.5		16.3
3	40.6		
5			66.6
6	50.1		
10	158	122	99.1
15	186		
20	238		
25	277	158	144
40	299		
50	194	126	127
75		114	124
100		118	128

[a] Values of 10^4 k_ψ, sec^{-1}.

for the specified pH. The results in Table VI, for example, show that the rate enhancements decrease with decreasing pH, and at these lower pH values we observe rate maxima in plots of k_ψ against C_D rather than plateaux.

The increasing protonation of the alkyl xanthate ion (I) in the presence of anionic micelles is easily understandable in terms of electrostatic interactions. There are no Coulombic interactions with nonionic micelles of Triton, but this surfactant should stabilize an undissociated alkylxanthic acid (II) relative to the more hydrophilic xanthate ion (I).

In the absence of surfactants plots of log k_ψ against pH are linear with slopes of −1 for decomposition of alkyl xanthates at pH > 2.5, but we do not observe this behavior in the presence of high concentrations of surfactants where these plots are curved, especially for CTABr and Triton (Figures 2–4). These experiments were carried out using relatively high surfactant concentrations, so that all the substrate should be taken up into the micelles.

There could be several reasons for this behavior. (1) Micelles affect the pH of buffered solutions by changing the acid dissociation constants,[14] and the substrates and buffer species will be distributed between the aqueous and micellar phases.[8-10] An uncharged alkylxanthic acid could be incorporated into a micelle, irrespective of its charge, especially if the alkyl group is hydrophobic, and the relatively hydrophobic *n*-octyl xanthate ion could be incorporated in anionic micelles of NaLS despite the electrostatic repulsions. (2) Micelles may change the rate of decomposition of

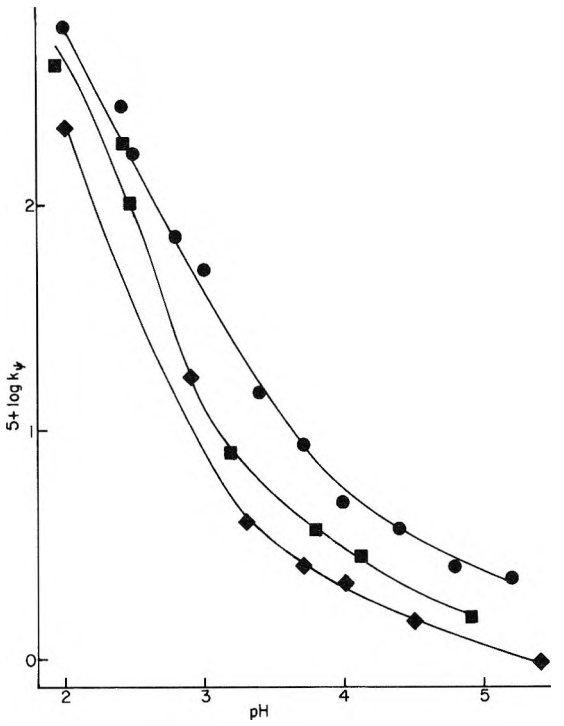


Figure 2. Variation of rate constant with pH in cationic micelles of CTABR: ●, ethyl xanthate in 5×10^{-3} M CTABr; ■, *n*-butyl xanthate in 2×10^{-3} M CTABr; ♦, *n*-octyl xanthate in 10^{-3} M CTABr.

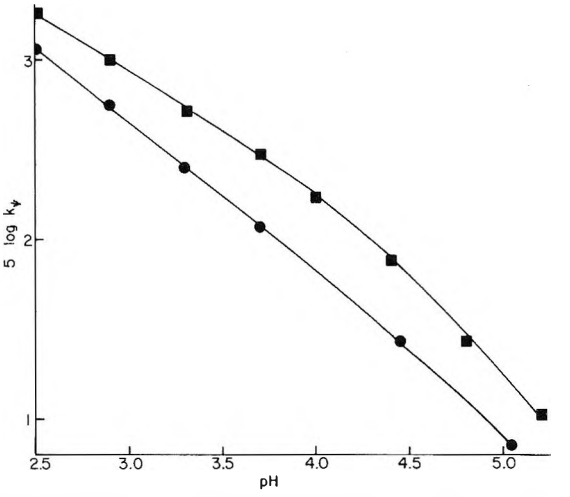


Figure 3. Variation of rate constant with pH in anionic micelles of 0.1 M NaLS: ●, ethyl xanthate; ■, *n*-butyl xanthate.

the xanthic acid (II). (3) There is a finite rate of reaction at high pH even in high concentrations of CTABr[15] (Figures 1 and 2), and when reaction is carried out in the presence of nonionic micelles of Triton X-100 the rates actually increase slightly at high pH (Figure 4). These observations are consistent with the appearance of a new reaction mechanism at high pH under these conditions. This reaction could be decomposition of the xanthate ion, which would generally be too slow to be observed but could be subject to catalysis by cationic and possibly nonionic micelles. However, anionic micelles should be ineffective in this role and we see no increase of reaction rate at high pH with micelles of NaLS (Figure 3).

$$ROCS_2^- \longrightarrow RO^- + CS_2$$

An additional problem arises from the difficulty of knowing the pH on the micellar surface as compared with

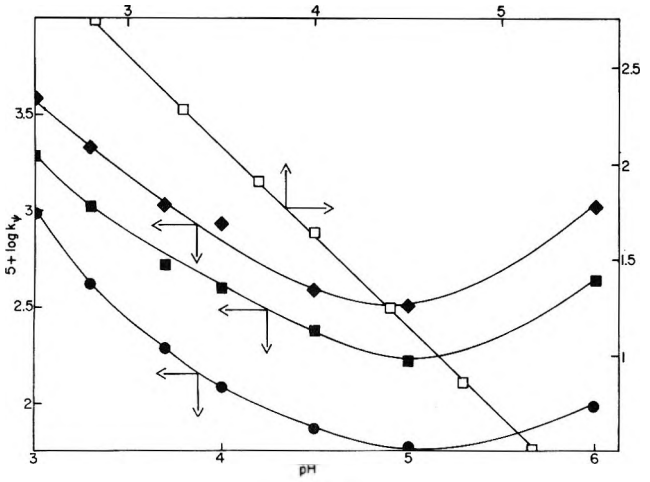


Figure 4. Variations of rate constant with pH in nonionic micelles of Triton: ●, ethyl xanthate; □ ■, *n*-butyl xanthate; ♦, *n*-octyl xanthate. The open points are for 5×10^{-4} *M* Triton and the solid points are for 10^{-2} *M* Triton.

that in the body of the solution,[16] and this problem is related to the appearance of rate maxima as shown in Table VI.

Micellar inhibition can generally be treated in terms of a partitioning of the substrate between the aqueous and micellar pseudophases,[8-10,17] and this treatment can occasionally be applied to micellar-catalyzed reactions.[18] However, these quantitative treatments cannot be applied to these xanthate reactions, in part for the reasons discussed above, but also because they require the assumption that changes in the critical micelle concentration (cmc) are small relative to the surfactant concentration. This approximation is a very dubious one for these reactions, because the relatively hydrophobic xanthic acid or xanthate ion could themselves promote micellization.

One major problem in studying micellar effects lies in deciding whether the micelles are acting by taking up the reactants, as is generally assumed, or whether they are merely affecting the properties of the solvent. With this in mind we observed that added sodium chloride in relatively high concentration decreases the inhibition by CTABr of the decomposition of *n*-butyl xanthate (Table VII) and increasing the concentration of acetate buffer has the same effect (Table VIII).[19] In the absence of surfactant the rate is almost unaffected by 10^{-2} *M* tetraethylammonium bromide. The salt effects upon the micellar inhibition could be caused either by exclusion of the substrate from the micelle, or by changes in micellar structure. The first explanation is generally applied to salt effects upon micellar catalysis and inhibition,[8-10] but changes in micellar structure are important in decarboxylations.[20]

Reaction at Low pH. An alkyl xanthate ion should be wholly protonated at pH < 1, so that micelles should affect the reaction rate only by changing the rate of decomposition of an alkylxanthic acid either directly, or indirectly by increasing the amount of the unreactive conjugate acid (IV). It is difficult to separate these factors, but decomposition of the xanthic acid is probably playing a role because in 0.1 *M* HCl anionic micelles of NaLS retard decomposition of *n*-butyl xanthate, and in 1 *M* HCl, where there should be some protonation of the xanthic acid,[21] reaction is also inhibited by NaLS. Nonionic micelles of Brij 58 have no effect on the reaction rate, which is consistent with this qualitative explanation, because they should not assist protonation of an alkylxanthic acid or its decomposition. However, CTABr slightly hinders reaction in 0.1 *M* HCl, suggesting that some *n*-butyl xanthate is then formed, but it catalyzes the reaction in 1 *M* HCl (Table IX) although the enhancement is relatively small (less than threefold). This rate enhancement is understandable if the transition state is between the zwitterion (III) and product, with favorable Coulombic interactions between the micelle and the CS_2^- group, and such a transition state should be destabilized by NaLS. Some support is given for this hypothesis by the rate enhancement of the reaction of the relatively hydrophobic *n*-octyl xanthate by CTABr, even in 0.1 *M* HCl, where in the absence of surfactants protonation of the xanthate ion should be almost complete, but there should be no protonation of the xanthic acid (Table X).

Table VII
Effect of Sodium Chloride on the Reaction of *n*-Butyl Xanthate in CTABr[a]

C_{NaCl}, *M*	$10^3 k_\psi$, sec^{-1}	C_{NaCl}, *M*	$10^3 k_\psi$, sec^{-1}
	0.033	0.10	0.31
0.001	0.051	0.15	0.42
0.005	0.063	0.20	0.51
0.01	0.076	0.50	0.92
0.025	0.11	1.00	1.40
0.05	0.20		

[a] At 25.0° in pH 3.89, 2×10^{-3} *M* CTABr and 0.02 *M* acetate buffer.

Table VIII
Effect of Sodium Acetate on the Reaction of *n*-Butyl Xanthate in CTABr[a]

C_{NaOAc}, *M*	$10^3 k_\psi$, sec^{-1}
0.0069	0.026
0.020	0.033
0.028	0.041

[a] At 25.0°, pH 3.89, and 2×10^{-3} *M* CTABr.

Table IX
Effect of Surfactants on the Acid Hydrolysis of *n*-Butyl Xanthate[a]

	NaLS		CTABr		Brij	
	C_{HCl}, *M*					
$10^3 C_D$, *M*	0.1	1.0	0.1	1.0	0.1	1.0
	98.0	96.0	98.0	96.0	98.0	96.0
1	82.0		82.0		93.0	
3	76.0	69.7	80.0	260	100	99.0
6	41.2					
8		41.2	80.7	302	103	103
16	26.0		80.5			
20					94.0	90.0
25	25.8					
30			83.0			
60			85.0			

[a] Values of $10^3 k_\psi$, sec^{-1}, at 25.3°.

Table X
Reaction of *n*-Octyl Xanthate in CTABr and 0.1 *M* HCl[a]

$10^3 C_{CTABr}$	$10^3 k_\psi$, sec^{-1}	$10^3 C_{CTABr}$	$10^3 k_\psi$, sec^{-1}
	34.9	16	62.7
3	39.2	30	67.2
8	53.3	60	72.2

[a] At 25.0°.

Table XI
Micellar Effects upon the Apparent Dissociation Constants of *n*-Butylxanthic Acid in Water

Surfactant	"pK_a"	Surfactant	"pK_a"
	1.54	5×10^{-2} *M* NaLS	2.45
2×10^{-3} *M* CTABr	1.01	10^{-2} *M* Triton	1.92

Micellized alkyl sulfates are readily hydrolyzed in moderately concentrated acid; therefore we did not use highly acidic solutions in these experiments, and freshly made solutions were always used.

Apparent Dissociation Constants. Micellar effects upon the rates at pH > 3 can be explained qualitatively in terms of changes in the acid dissociation of the alkylxanthic acid. Similar observations have been made on a number of micellar catalyzed or inhibited reactions.[8-10,14b] We have calculated the apparent dissociation constant of *n*-butylxanthic acid in the presence of micelles by rapidly determining the total concentration of xanthate ion. (The values are apparent because we do not know the distribution of xanthic acid or xanthate and hydronium ions between water and the micellar pseudophase.[16])

Micelles change the dissociation constant in the expected directions (Table XI). Cationic micelles of CTABr should stabilize the xanthate ion relative to xanthic acid, and they increase the dissociation constant, whereas anionic micelles of NaLS and nonionic micelles of Triton should stabilize xanthic acid relative to its anion, and they decrease the dissociation constant.

Registry No.—Ethyl xanthate, 151-01-9; *n*-butyl xanthate, 110-50-9; *n*-octyl xanthate, 6253-37-8; CTABr, 57-09-0; NaLS, 151-21-3; Triton X-100, 9002-93-1.

References and Notes

(1) Support of this work by the National Science Foundation, The Comision Central de Investigacion of the University of Chile, and the University of Chile–University of California Cooperative Program supported by the Ford Foundation is gratefully acknowledged.
(2) For a general discussion of xanthate chemistry and the industrial applications of alkyl xanthates, see ref 3.
(3) S. R. Rao, "Xanthates and Related Compounds," Marcel Dekker, New York, N. Y., 1971.
(4) I. Iwasaki and S. R. B. Cooke, *J. Amer. Chem. Soc.*, **80**, 285 (1958); *J. Phys. Chem.*, **63**, 1321 (1959); **68**, 2031 (1964).
(5) E. Klein, J. K. Bosarge, and I. Norman, *J. Phys. Chem.*, **64**, 1666 (1960).
(6) C. A. Bunton, P. Ng, and L. Sepulveda, *J. Org. Chem.*, **39**, 1130 (1974).
(7) For reviews of micellar catalysis and inhibition, see ref 8–10.
(8) E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).
(9) E. H. Cordes and C. Gitler, *Progr. Bioorg. Chem.*, **2**, 1 (1973).
(10) C. A. Bunton, *Progr. Solid State Chem.*, **8**, 239 (1973).
(11) A. I. Vogel, "Practical Organic Chemistry," Wiley, New York, N. Y., 1956.
(12) Alkylxanthic acids have $pK_a \sim 1.5$.[3-6]
(13) By pH we mean the value in the reaction mixture as measured using a glass electrode.
(14) (a) L. K. J. Tong and M. C. Glesmann, *J. Amer. Chem. Soc.*, **79**, 4305 (1957); (b) M. T. A. Behme and E. H. Cordes, *ibid.*, **87**, 260 (1965); (c) C. A. Bunton and M. J. Minch, *J. Phys. Chem.*, **78**, 1490 (1974).
(15) The residual rate at high concentrations of CTABr decreases with increasing length of the *n*-alkyl group of the xanthate, probably because the longer alkyl groups tend to take the substrate more deeply into the micelle.
(16) C. A. Bunton and B. Wolfe, *J. Amer. Chem. Soc.*, **95**, 3742 (1973).
(17) F. M. Menger and C. E. Portnoy, *J. Amer. Chem. Soc.*, **89**, 4968 (1967).
(18) C. A. Bunton, E. J. Fendler, L. Sepulveda, and K.-U. Yang, *J. Amer. Chem. Soc.*, **90**, 5512 (1968).
(19) Salt and buffer effects are very small in the absence of surfactants.[4-6]
(20) C. A. Bunton, M. J. Minch, J. Hidalgo, and L. Sepulveda, *J. Amer. Chem. Soc.* **95**, 3262 (1973).
(21) For the equilibrium II $\rightleftarrows$ IV $pK_a \simeq -1$.[4,6]

Kinetics of the Condensation of *N*-Methyl-4-picolinium Iodide with *p*-Dimethylaminobenzaldehyde in Aqueous Ethanol

David N. Kramer,* Lawrence P. Bisauta, and Robert Bato

Chemical Laboratory, Edgewood Arsenal, Aberdeen Proving Ground, Maryland 21010

Brown L. Murr, Jr.

Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218

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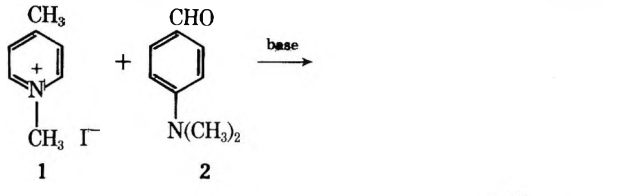
The kinetics of condensation of *N*-methyl-4-picolinium iodide and *p*-dimethylaminobenzaldehyde in 78.2% (v:v) aqueous alcoholic sodium hydroxide were determined at 25° spectrophotometrically by following the appearance of *p*-dimethylamino-4-styrylpyridinium methiodide at 470 nm. The reaction was first order in methiodide, aldehyde, and hydroxide with a third-order rate constant of $1.67 \times 10^{-2}\ M^{-2}\ \text{sec}^{-1}$. The kinetics of the proton exchanges of *N*-methyl-4-picolinium iodide in methanol-d_4–methoxide-d_3 were determined by nmr at 35°. The second-order rate constants for exchange of *N*-methyl, 2,6-, and *C*-methyl protons were 2.2×10^{-5}, 1.62×10^{-4}, and $7.5 \times 10^{-2}\ M^{-1}\ \text{sec}^{-1}$, respectively. The second-order rate constant for the *N*-methyl proton exchange of *N*-methylpyridinium iodide was $16 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$. The kinetic data are in accord with a condensation mechanism in which the rate-determining step is carbon–carbon bond formation by reaction of the methylene base with the aldehyde. Nitrogen decoupling experiments showed the β protons of the *N*-methylpyridinium iodide to be coupled to nitrogen. Furthermore, the *N*-methyl group showed a positive nuclear Overhauser effect upon irradiation of nitrogen.

In conjunction with a study of the detection of alkyl halides by reaction with 4-picoline we have examined the rate of the 78.2% (v:v) aqueous alcoholic base induced condensation of *N*-methyl-4-picolinium iodide (**1**) with *p*-dimethylaminobenzaldehyde (**2**) to yield the highly colored *p*-dimethylamino-4-styrylpyridinium methiodide (**3**) (eq 1). Phillips[1] has reported the analogous piperidine-induced condensation of *N*-methyl-2-picolinium iodide with **2**.

The objective of the kinetic experiments was to determine the reaction mechanism sufficiently to define the optimum conditions for alkyl halide detection. The central mechanistic questions were (1) the role of the conjugate

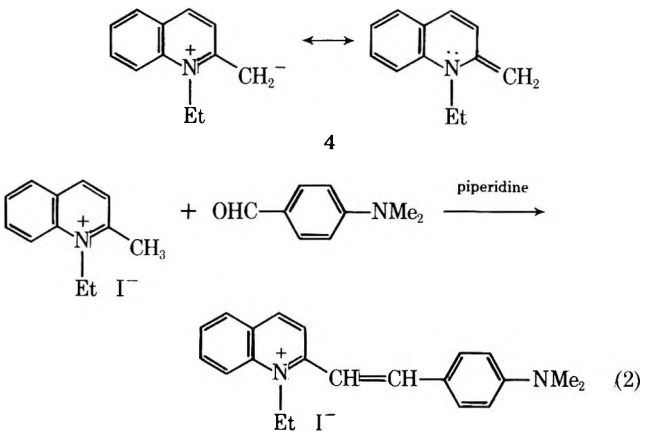
base of the quaternary ammonium ion (*i.e.*, the methylene base); (2) the role of the dimer of the methylene base; and (3) the identification of the rate-determining step of dye production, whether it is carbon–carbon bond formation or



1 2 3 (1)

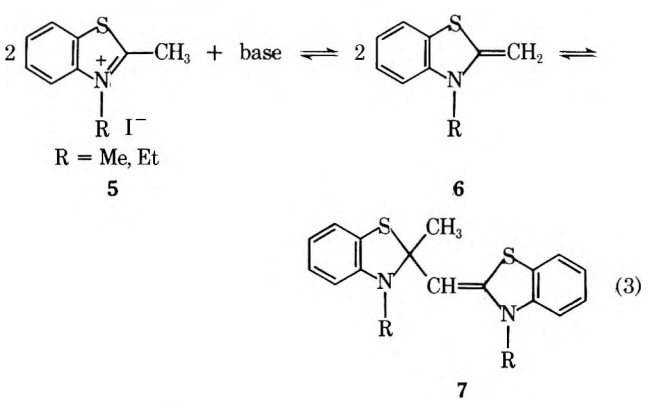
elimination to form the final conjugated system. In ancillary experiments we have measured the rates of exchange of the protons of **1** in methanol-d_4–methoxide-d_3.

Mills and Raper[2] suggested methylene base **4** as an intermediate in the piperidine-catalyzed reaction of 1-ethylquinaldinium iodide with **2** (eq 2).



4 (2)

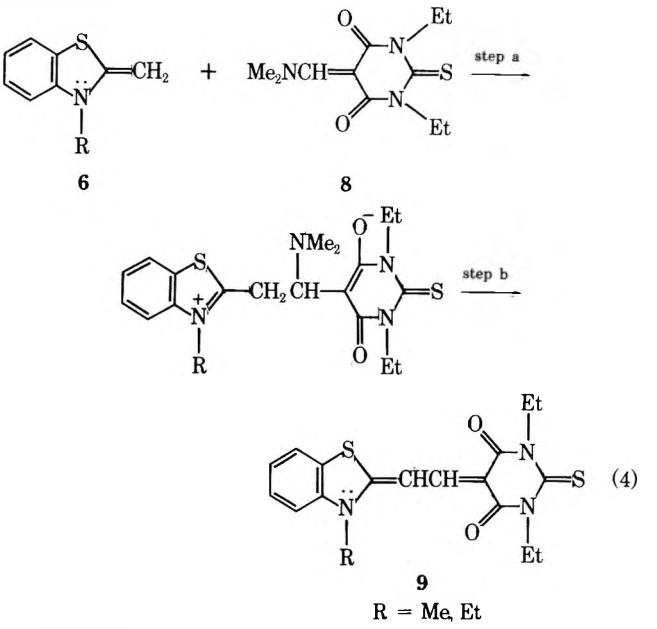
Although Mastagli, Larivé, and Etevenon[3] presented evidence that methylene base **6** is not necessarily an intermediate in the condensation (eq 3) in neutral and acidic media, Brooker[4] invoked methylene base **6** to account for his observations on the condensation of 2-methyl-3-alkylbenzothiazolium iodide (**5**) with **2**. The latter system introduces a complication in that **6** has been shown to form **7** and this dimer can serve as a source of monomeric methylene base **6**. The dimer apparently forms by reaction of methylene base with quaternary salt.[5] In elegant experiments Owen[5] isolated the monomeric methylene base **6**. This isolation made possible a study of the monomer–dimer equilibrium. Although no data were presented on the rate of approach to equilibrium in solution, the monomer (presumably neat) dimerized within 2 hr at 0° under nitrogen. Spectra of the monomer could be determined without interference from dimerization.[5]



R = Me, Et

5 6 7 (3)

Owen[5] also studied the rate of condensation of methylene base **6** with 1,3-diethyl-5-(*N*,*N*-dimethylaminomethylene)-2-thiobarbituric acid (**8**) in acetonitrile containing triethylamine (eq 4).[5] He concluded that carbon–carbon



6 8 9 (4)

R = Me, Et

bond formation (eq 4, step a) was rate determining because the condensation rate was independent of the concentration of excess triethylamine presumably necessary for step b. Furthermore, the rate of formation of **9** from quaternary salt **5** in the presence of a 1000-fold excess of **8** and a 10,000-fold excess of triethylamine was identical within experimental error with the rate of formation of **9** using methylene base **6**. This result would suggest that quaternary salt is converted completely to methylene base by triethylamine in a step that is not rate controlling. It seems safe to conclude that dimerization of methylene base is not kinetically significant under Owen's conditions; otherwise the reaction would approach one-half order, instead of the observed first order in methylene base.

While the above-mentioned studies provide an informative guide to the individual steps that might be involved in the condensation in aqueous ethanol, they are at best only suggestive regarding the rate-determining step. We, therefore, have examined the kinetic form of the condensation reaction along with the rates of proton exchange of *N*-methyl-4-picolinium iodide (**1**) in methanol-d_4–methoxide-d_3 to estimate the rate of formation of methylene base derived from **1**.

Results

Kinetics of Condensation. The product of the condensation of **1** and **2** in 78.2% (v:v) aqueous ethanolic sodium hydroxide was **3**. This structural assignment was based on melting point comparison (mp 256–258°, lit. mp 255°)[6] and nmr spectral data. Compound **3** showed resonances at δ 4.28 (s, 3 H, N^+CH_3) and 3.2 [s, 6 H, $N(CH_3)_2$], and complex absorptions at δ 6–7. There were no resonances at higher field than δ 3.2 in the product **3**, indicating the absence of an aromatic methyl group. The *N*-methyl-4-picolinium iodide showed resonances at δ 1.9 (s, 3 H, CCH_3) and 3.6 (s, 3 H, N^+CH_3). Nitrogen decoupling experiments showed that it was the signal of the β protons of **1** that was broadened considerably by nitrogen coupling. This broadening, which is characteristic of *N*-alkylpyridinium salts, is absent in the free basis. Irradiation of the nitrogen shows a nuclear Overhauser effect for the NCH_3 group, the methyl intensity increasing about 13%. Thus, the nmr spectrum of

Table I
Initial Rate Studies of Reaction Order and the Derived Third-Order Rate Constants for the Base-Catalyzed Condensation of *N*-Methyl-4-picolinium Iodide and *p*-Dimethylaminobenzaldehyde at 25°, 78.2% Aqueous Ethanol (v: v)

[Methiodide], 10^4 *M*	d(OD)[a]/dt, min^{-1}	[OH^-]	10^2 [aldehyde], *M*	$10^2 k_3$,[b] M^{-2} sec^{-1}
0.2	0.013	1.0	2.0	1.63
0.5	0.031	1.0	2.0	1.55
1.0	0.058	1.0	2.0	1.46
1.5	0.080	1.0	2.0	1.33
2.0	0.114	1.0	2.0	1.43
1.0	0.013	1.0	0.5	1.31
1.0	0.028	1.0	1.0	1.41
1.0	0.042	1.0	1.5	1.41
1.0	0.060	1.0	2.0	1.51
2.0	0.026	0.25	2.0	1.30
2.0	0.044	0.375	2.0	1.47
2.0	0.062	0.5	2.0	1.55
2.0	0.119	1.0	2.0	1.49
			Average	1.46 ± 0.15

[a] Initial slope of the trace of optical density *vs.* time. [b] Using an extinction for dye 3 of 3.32×10^4 M^{-1} cm^{-1}.

3 was consistent with condensation at the 4-methyl group and clearly inconsistent with condensation at the *N*-methyl group.

The kinetic order of each factor in the base-catalyzed condensation of 1 and 2 in aqueous ethanol was determined spectrophotometrically by following the rate of appearance of the 470-nm band of **3**. The initial slope of the trace of optical density *vs.* time was divided by the extinction coefficient for **3** (ϵ 3.32×10^4 M^{-1} cm^{-1}) to obtain the initial rate of formation of **3**. In any given run the concentration of base was constant. The concentration of **2** was always at least 50 times that of **1**, and thus its concentration remained constant. From the behavior of the initial rates as a function of the concentrations of base, aldehyde, and methiodide, the reaction was shown to be first order within experimental error in each of these reagents. The third-order rate constants derived from the initial rates are shown in Table I. The average value of the third-order rate constant from the initial rate data was 1.46×10^{-2} M^{-2} sec^{-1}.

The reaction was also followed through 1 half-life (or a portion thereof at higher concentrations of **1**). Values of optical density and time were read from the trace and optical densities at infinite time were obtained by dilution. Point-by-point pseudo-first-order rate constants were calculated from eq 5 where ($OD_\infty - OD_0$) is proportional to the initial methiodide concentration and ($OD_\infty - OD_t$) is proportional to methiodide at time *t*. The pseudo-first-order rate constants were divided by the appropriate hydroxide and aldehyde concentrations to obtain third-order rate constants. Comparison of the third-order rate constants from initial rate studies (Table I) and those from point-by-point determinations (Table II) shows satisfactory agreement.

$$k = \frac{1}{t} \ln \left[\frac{OD_\infty - OD_0}{OD_\infty - OD_t} \right] \quad (5)$$

Proton Exchange of *N*-Methyl-4-picolinium Iodide. For convenience the rates of proton exchange of *N*-methyl-4-picolinium iodide (**1**) were determined in methanol-d_4 containing methoxide-d_3. the rates were followed by observing the decay of the nmr signal characteristic of a particular proton. All protons in **1** were exchangeable. The extent of exchange was determined by integration of the particular signal relative to the carbon-bound proton impurity in methanol-d_4 as a standard. The exchange measurements were carried out at 35°.

Table II
Point-by-Point Pseudo-First-Order Rate Constants and Derived Third-Order Rate Constants for the Base-Catalyzed Condensation of *N*-Methyl-4-picolinium Iodide and *p*-Dimethylaminobenzaldehyde at 25°

[Methiodide], 10^4 *M*	[Aldehyde], 10^2 *M*	$10^4 k_{obsd}$,[a] sec^{-1}	$10^2 k_3$, M^{-2} sec^{-1}
2	2	3.42	1.72
2	2	3.27	1.63
1	1	1.75	1.75
1	1	1.58	1.59
		Average	1.67 ± 0.08

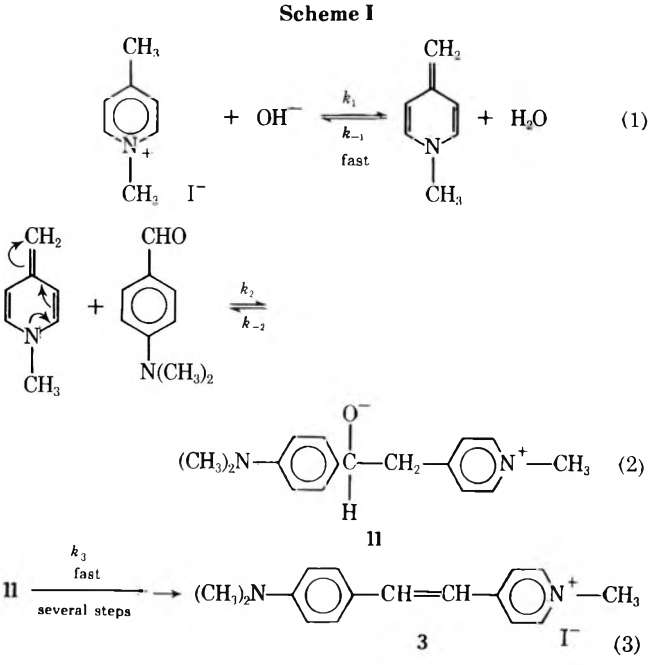
[a] [OH^-] = 1.0 *M* in all runs; solvent 78.2% ethanol (v:v).

The 4-methyl proton of **1** exchanged too rapidly to measure in 1.47 *M* methoxide-d_3 in methanol-d_4. Under these conditions the *N*-methyl protons (δ 4.40) exchanged with a pseudo-first-order rate constant of 3.3×10^{-5} sec^{-1} corresponding to a second-order rate constant of 2.2×10^{-5} M^{-1} sec^{-1}. The rate constant of *N*-methylpyridinium iodide determined similarly was 16×10^{-5} M^{-1} sec^{-1}. The inductive effect of the 4-methyl group retards the rate almost eightfold. The rate of exchange of the 2,6 protons of **1** was about ten times faster than that of its *N*-methyl protons, showing a second-order rate constant of 1.62×10^{-4} M^{-1} sec^{-1} in 0.8 *M* methoxide-d_3–methanol-d_4. The 4-methyl protons exchanged with a second-order rate constant of 7.5×10^{-2} M^{-1} sec^{-1} in 1.47×10^{-4} *M* methoxide-d_3–methanol-d_4.

Discussion

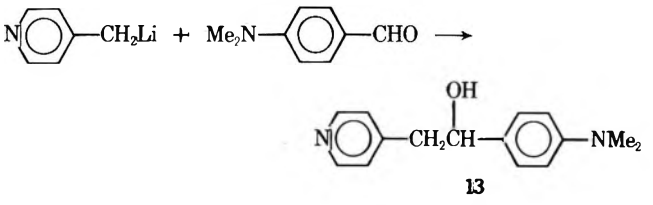
The simplest mechanism that is consistent with the kinetic data is shown in Scheme I in which $k_{-2} \ll k_3$. The appearance of the aldehyde in the rate expression suggests

Scheme I



that proton transfer (step 1) cannot be rate determining. This conclusion was confirmed by the nmr exchange experiments, that showed that the 4-methyl protons of *N*-methyl-4-picolinium iodide exchanged much faster than the formation of product **3**. The first-order dependence of the condensation rate on base shows that the equilibrium constant for step 1 must be small; *i.e.*, an inappreciable amount of *N*-methyl-4-picolinium iodide is converted to methylene base. In the extreme case, if all picolinium iodide were converted to methylene base, then an increase in the concentration of base would not increase the rate. The conclusion was checked by showing that the uv spectrum of *N*-methyl-4-picolinium iodide was the same in the presence and absence of 1 *M* base. Thus, all of the evidence is consistent with a rapid proton-transfer equilibrium, with step 2 rate determining. Methylene base dimer is not a kinetically significant intermediate.

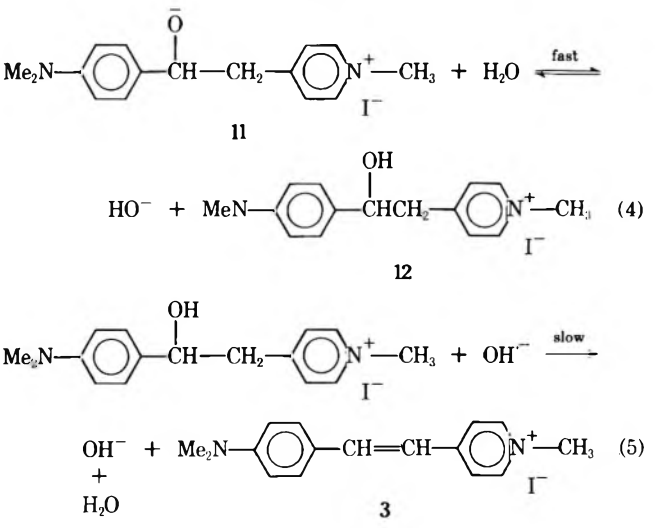
Another mechanism can be shown to be consistent with the kinetic data if step 3 (Scheme I) is expanded to include the individual steps involved (Scheme II). Thus, if steps 1, 2 (Scheme I), and 4 are rapid and reversible and step 5 (Scheme II) is rate determining, third-order kinetics would result. This mechanism is analogous to that of the condensation of acetophenone with benzaldehyde in ethoxide–ethanol, where it has been shown that the keto alcohol is degraded to acetophenone and benzaldehyde more rapidly than it is converted to benzalacetophenone.[7] To probe this possibility we prepared the alcohol **13** by reaction of the lithium salt of 4-methylpyridine with *p*-dimethylaminobenzaldehyde.[8] Reaction of **13** with methyl iodide failed to



13

produce **12** in pure form. However, treatment of the solution prepared from **13** and methyl iodide with base gave 10% **3** (based on **13**) but less than 1% **2**, which was the limit of spectrophotometric detectability of **2**. Thus, the balance of the evidence suggests that condensation step 2 is rate determining and not the dehydration step.

Scheme II



Our results show that the condensation reaction is substantially faster than the alkylation of 4-picoline by methyl iodide.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 in potassium bromide. Routine nmr spectra were determined on a Varian A-60D instrument. Ultraviolet spectra were run on a Cary Model 14 spectrophotometer or a Beckman DB spectrophotometer.

***N*-Methyl-4-picolinium methiodide** was obtained by refluxing equimolar quantities of 4-picoline (Eastman) and methyl iodide in ethanol for 24 hr in the dark. Recrystallization from ethanol afforded material with mp 152° (lit. mp 152°).[9]

***p*-Dimethylamino-4-styrylpyridinium methiodide** was prepared by refluxing 2.34 g (0.01 mol) of *N*-methyl-4-picolinium iodide and 1.5 g (0.01 mol) of dimethylaminobenzaldehyde (Eastman) in ethanol containing 0.03 mol of sodium ethoxide for 1 hr. Upon cooling red needles separated, which were crystallized from ethanol, mp 256–258°. *Anal.* Calcd for $C_{16}H_{19}N_2I$: C, 52.46; H, 5.19; N, 7.65; I, 34.7. Found: C, 52.48; H, 5.17; N, 7.37; I, 34.8. The nmr, ir, and uv–visible spectral data were in accord with the assigned structure. The extinction coefficient for the styryl methiodide in 95% ethanol was $5.16 \times 10^4\ M^{-1}\ cm^{-1}$ at 470 nm.

1-(4-Dimethylaminophenyl)-2-(4-pyridyl)ethanol (13) was prepared by a modification of Villani's method[8] using *n*-butyllithium in tetrahydrofuran instead of sodium amide. To 15 ml of a 22% hexane solution of *n*-butyllithium (0.035 mol) at 4° was added dropwise 3.3 g (0.036 mol) of 4-picoline in 20 ml of tetrahydrofuran. After 30 min 4.5 g (0.03 mol) of *p*-dimethylaminobenzaldehyde in 20 ml was added dropwise at 5°. The clear yellow solution was allowed to stand for 18 hr after which time 50 ml of water was added. The solution was extracted with benzene. The resulting solution was dried with magnesium sulfate and the solvent was removed by rotary evaporation. The residue was recrystallized twice from benzene. The product (1 g) had mp 166–168° (lit. mp 165–167).[8]

Kinetics. Stock solutions of *N*-methyl-4-picolinium iodide and *p*-dimethylaminobenzaldehyde were prepared in absolute ethanol. Stock solution of potassium hydroxide were prepared in distilled water. The concentrations of the stock solutions were adjusted so that combination of 0.9 ml of the iodide and aldehyde solutions with 0.5 ml of the aqueous base gave the final concentration of reactants shown in Tables I and II. A run was initiated by addition of temperature-equilibrated base to a cuvette containing iodide and aldehyde. The resulting solution was shaken vigorously and placed in the thermostated compartment of the spectrophotometer.

The initial rate studies (Table I) were carried out on a Beckman DB instrument. Tangents were drawn to the curve and the slopes were determined in the usual way. Corrections were applied where necessary for any reaction that had occurred before the optical density traces could be started. The correction was determined from the initial optical density, the extinction coefficient of the dye, and the stoichiometric concentrations. The experiments were done several times. The results in Table I are representative.

Point-by-point rate data were determined on a Cary 14 instrument. The procedure for preparation and mixing of stock solutions was the same as that for the initial rate studies. The trace of optical density against time was followed from 10 min to 1 hr. The solutions were incubated for 8–10 half-lives before the final optical density reading was taken. Pseudo-first-order rate constants were reproducible to ±5%.

Proton Exchange of *N*-Methyl-4-picolinium Iodide with Methanol-d_4–Methoxide-d_3. Sodium metal (67.7 mg, 3 mmol) was dissolved in 2 ml of methanol-d_4 (E & M Laboratories, Inc., 99% D, 98.5% CD_3) to give a 1.5 *M* solution. Addition of 35.5 mg (0.15 mmol) of *N*-methyl-4-picolinium iodide to 0.5 ml of the basic methanol-d_4 solution produced a dark green solution. The nmr spectrum showed complete loss of 2,6 aromatic resonance at δ 8.81 (doublet, 2 H) and the high-field methyl resonance at δ 3.68 (singlet, 3 H). The high-field aromatic doublet at δ 7.95 had collapsed to a broad singlet. The exchanged protons appeared in the solvent peak at δ 6.13.

The low-field methyl resonance at δ 4.40 exchanged slowly. The rate was determined by periodic integration of the peak using the carbon-bound proton impurity in methanol-d_4 as a standard. The 3 and 5 protons also exchanged but more slowly. The rate of exchange of the 2,6 protons was determined similarly in 0.8 *M* methoxide. For comparison the rate of exchange of the *N*-methyl protons in *N*-methylpyridinium iodide was determined in a similar manner.

The rate of exchange of 4-methyl protons was determined in 1.47×10^{-4} *M* base by integration of the singlet at δ 3.68 using the *N*-methyl signal as standard.

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Registry No.—**1**, 2301-80-6; **2**, 100-10-7; **3**, 959-81-9.

References and Notes

(1) A. P. Phillips, *J. Org. Chem.*, **12**, 333 (1947).
(2) W. Mills and R. Raper, *J. Chem. Soc.*, 2460 (1925).
(3) P. Mastagli, H. Larivé, and P. Etevenon, *C. R. Acad. Sci.*, **252**, 3782 (1961).
(4) L. G. S. Brooker, S. G. Dent, Jr., D. W. Heseltine, and E. Van Large, *J. Amer. Chem. Soc.*, **75**, 4335 (1953), and earlier papers in the series.
(5) J. R. Owen, *Tetrahedron Lett.*, 2709 (1969); *Eastman Org. Chem. Bull.*, **43**, No. 3 (1971).
(6) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 1454 (1938).
(7) D. S. Noyce, W. A. Pryor, and A. H. Battini, *J. Amer. Chem. Soc.*, **77**, 1402 (1955).
(8) F. J. Villani, C. A. Ellis, and S. Tolksdorf, *J. Med. Chem.*, **13**, 359 (1970).
(9) "Chemistry of Carbon Compounds," Vol. 4A, E. H. Rodd, Ed., American Elsevier, New York, N. Y., 1957, p 523.

Notes

N-Monochlorination and N-Monobromination of Carbamates and Carboxamides by Sodium Hypochlorite and Hypobromite[1a]

Carol Bachand, Hughes Driguez,[1b] John M. Paton,[1c] Daniel Touchard,[1d] and Jean Lessard*

Département de Chimie, Université de Sherbrooke, Sherbrooke, Québec, J1K 2R1, Canada

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Our studies on the chromous chloride promoted addition of *N*-chlorocarbamates to olefins[2] led us to devise a convenient method for the preparation of *N*-monochlorocarbamates in high yield, free from the *N,N*-dichloro derivatives. This method was also applied to the preparation of *N*-monochlorocarboxamides and of *N*-monobromocarbamates and -carboxamides needed for the chromous chloride promoted addition studies[2c] and some photochemical work.[3] The recent publication of Swern and coworkers[4] on the preparation of ethyl and methyl *N*-chlorocarbamates prompted us to report our results.

The method consists of the formation of the sodium salt of the monohalo derivative followed by careful neutralization. The salt is prepared by treating a slight excess (0.5–2%) of the amide with sodium hypochlorite or hypobromite[5] (5–6% solution) at *ca.* 0° (eq 1). After the addition of

$$ZCONH_2 + NaOX \longrightarrow ZCONXNa + H_2O \quad (1)$$

$$ZCONXNa + H_3O^+ \longrightarrow ZCONHX + H_2O + Na^+ \quad (2)$$

methylene chloride, dilute (1–2 *N*) sulfuric acid is added slowly until the sodium salt (eq 2) and the excess sodium hydroxyde are neutralized (an excess of acid must be avoided). The solvent is removed at reduced pressure at 20–25°. The results are recorded in Table I.

***N*-Chlorocarbamates.** The yields of the *N*-monochlorocarbamates **1**–**6**[7] are excellent (86–98%) with the purity of the crude reaction products being satisfactory for use in reactions without further purification. The method is thus very efficient.

***N*-Chlorocarboxamides.** The *N*-monochlorocarboxamides **8**–**16** were obtained in good yield, the purity of the crude reaction products being satisfactory for use in reactions. The method was not successful with the sterically hindered 2,2-dimethylpropionamide nor was it convenient for the preparation of the water-soluble *N*-chloroformamide (**7**). Beckwith and Goodrich[8] have prepared *N*-monochlorocarboxamides in good yield by the bromine-catalyzed reaction of primary carboxamides with *tert*-butyl hypochlorite.

***N*-Bromocarbamates.** We have studied the bromination of ethyl, 2,2,2-trichloroethyl, and benzyl carbamates (**17**, **18**, and **19**) and, to our knowledge, this is the first reported preparation of *N*-bromocarbamates. It appears that the disproportionation of the *N*-bromocarbamates **17** and **18** (eq 3) does occur to a significant extent ($K^{eq} \simeq 0.08$ and

$$2ROCONHBr \rightleftharpoons ROCONH_2 + ROCONBr_2 \quad (3)$$

0.1, respectively, at *ca.* 37°). Indeed, although both the iodometric and neutralization analyses of the crude *N*-bromocarbamates **17** and **18** indicated a purity of 100%, their ir and nmr spectra showed the presence of nonbrominated carbamate. A careful examination of the integration for the various protons of the nmr spectra indicated clearly the presence of a third product, most probably the *N,N*-dibromocarbamate, the aliphatic protons of which had the same chemical shift as those of the *N*-monobromocarbamate, the molar ratio being approximately equal to that of the nonbrominated carbamate (see Experimental Section for details).

The crude benzyl *N*-bromocarbamate (**19**) was found to decompose rapidly under reduced pressure, as evidenced by continuous evolution of gas within the oily product, the loss of active bromine, and reduction in weight of material (the yield and active bromine content reported in Table I refer to a crude product kept under reduced pressure for 10 min after evaporation to dryness). The crude *N*-bromocarbamates **17**, **18**, and **19** could be stored in the refrigerator for several days without any loss of active bromine.

***N*-Bromocarboxamides.** Kergomard[6] has prepared *N*-bromoacetamide by adding a sodium hypobromite solution[5] to a solution of acetamide in acetic acid. *N*-Bromobenzamides have been prepared by using bromine in aqueous alkaline solution with subsequent rapid acidification

Table I
Preparation of *N*-Haloamides

N-Halo amide	(No.)	Yield,[a] %	Purity, % of theory: Iodometric	Purity, % of theory: Neutralization	% starting amide[b]	Mp, °C: Crude	Mp, °C: Purified[c]	Mp, °C: Lit.	Registry no.
$CH_3CH_2OCONHCl$	(1)	98	99	100		17–19		9[d]	51-79-6
$CH_3CH_2CH_2OCONHCl$	(2)	86	98			Oil			
$CH_3OCH_2CH_2OCONHCl$	(3)	93	96			Oil			
$ClCH_2CH_2OCONHCl$	(4)	91	96	98		53–55	56.5–57.5	42[e]	
$Cl_3CCH_2OCONHCl$	(5)	92	98	99		61–63	63–63.5		
$C_6H_5CH_2OCONHCl$	(6)	98	98	99		27–29			621-84-1
$HCONHCl$	(7)	50	86			Oil			75-12-7
$CH_3CONHCl$	(8)	70[f]	100				109–110	110[g]	60-35-5
$CH_3CH_2CONHCl$	(9)	78	94	95		Oil			79-05-0
$ClCH_2CH_2CONHCl$	(10)	88	96			69–74	74–74.5		5875-24-1
$BrCH_2CONHCl$	(11)	80	101			67–68	68.5–69		683-57-8
$ClCH_2CONHCl$	(12)	83	98	100		66–68	68–69.5		79-07-2
$FCH_2CONHCl$	(13)	79	101			98.5–100	100.5–101		640-19-7
$Cl_2CHCONHCl$	(14)	81	101			70–71	70–71		683-72-7
$Cl_3CCONHCl$	(15)	85	99			120–122	122–123		594-65-0
$F_3CCONHCl$	(16)	63	99			Oil[h]			354-38-1
$CH_3CH_2OCONHBr$	(17)	85	100	101	~10	Oil			
$Cl_3CCH_2OCONHBr$	(18)	92	100	101	~13	Oil			
$C_6H_5CH_2OCONHBr$	(19)	79	83		~15	Oil			
$CH_3CH_2CONHBr$	(20)	87	100	100		74–75	76–77		
$CH_3CH_2CH_2CH_2CONHBr$	(21)	80	94	96		Oil			626-97-1
$ClCH_2CH_2CONHBr$	(22)	89	97			87–88	89–90		
$BrCH_2CONHBr$	(23)	78	99	100		103–104.5			
$ClCH_2CONHBr$	(24)	79	98	98	~4	74–76	77–78	75[i]	
$FCH_2CONHBr$	(25)	65	99		~6	82–83	83.5–84		
$Cl_2CHCONHBr$	(26)	57	83		~18	73–77	94.5–95.5	96[i]	
$Cl_3CCONHBr$	(27)	45	77			95–97[j]		125[i]	
$F_3CCONHBr$	(28)	19	52					62[i]	

[a] Of active halogen compound before purification, based on the amide. [b] Starting amide present in the crude product as determined by nmr. [c] By recrystallization from methylene chloride or methylene chloride–hexane mixtures (iodometric purity >99%). [d] D. Saika and D. Swern, *J. Org. Chem.*, **33**, 4548 (1968). [e] P. Chabrier, *C. R. Acad. Sci.*, 214, 353 (1942). [f] Of recrystallized product. [g] K. J. P. Orton and A. E. Bradfield, *J. Chem. Soc.*, 986 (1927). [h] Crystalline in the refrigerator. [i] Reference 10. [j] The active bromine content was not significantly increased by recrystallization: 82%, mp 96–98°.

using acetic acid.[9] Our procedure gave better yields for the preparation of *N*-bromopropionamide (**20**) and *N*-bromopentanamide (**21**) and we have used it successfully also to prepare the *N*-bromocarboxamides **22–25.** The method is not convenient for the N-bromination of the dichloro-, trichloro-, and trifluoroacetamides (**26, 27,** and **28**), the yield and the purity of the crude product decreasing in the order **26** > **27** > **28.** Park, *et al.*,[10] has used bromine and silver oxide in anhydrous trifluoroacetic acid to prepare *N*-bromo-α-haloacetamides in good yield and Beebe and Wolfe[11] have obtained *N*-bromotrifluoroacetamide (**26**) in high yield using acetyl hypobromite.

In comparison to the *N*-bromocarbamates, the *N*-bromocarboxamides have much less tendency to undergo disproportionation into the carboxamide and the *N,N*-dibromo derivative. In the ir and nmr spectra of the pure (>99%) samples of the *N*-bromo-α-haloacetamides **23–26,** there is a small but detectable amount (2–4%) of nonbrominated carboxamide.[12]

Experimental Section[14]

Melting points were determined on a Büchi apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer spectrophotometer, Model 257. Nmr spectra were determined on a Varian A-60 spectrometer using TMS as internal standard. The sodium hypochlorite solution was obtained from Anachemia Chemicals Ltd.[15] and contained between 5.0 and 5.7% active chlorine (0.67–0.77 mmol/ml) and excess sodium hydroxide (~0.15 mmol/ml). The carbamates and carboxamides, unless specified otherwise, were obtained from Aldrich Chemical Co.

Iodometric Analyses. The samples (about 1 mmol accurately weighed) were dissolved in 50 ml of a 50:50 mixture of methanol and water. An excess of potassium iodide dissolved in water (5 ml) was added followed by sulfuric acid (1 ml of a 4 *N* solution). The solution was then titrated with 0.1 *N* sodium thiosulfate.

Neutralization Analyses. The samples (about 1 mmol accurately weighed) were dissolved in a 10:40 mixture of methanol and water. The solution was cooled in an ice bath and titrated with 0.1 *N* NaOH using a pH meter.

Preparation of *n*-Propyl, 2-Methoxyethyl, 2-Chloroethyl, and 2,2,2-Trichloroethyl Carbamate (29, 30, 31, and 32). These compounds were prepared from the corresponding alcohols according to the procedure described by Loev and Kormendy:[16] **29,** 65% yield (crude), mp 49–52° (lit.[17] mp 52.5°); **30,** 55% yield (crude), mp 44–46° (lit.[18] mp 46.8°); **31,** 33% yield (crude), mp 71–73° (lit.[19] mp 77°); **32,** 40% yield (recrystallized), mp 63–64°, ir ($CHCl_3$) 3540, 3430, 2940, 1750, 1585, 1385, 1325, 1115, and 1050 cm^{-1}, nmr ($CDCl_3$) δ 4.70 (s, 2 H), 5.62 (broad s, 2 H).

Anal. Calcd for $C_3H_4Cl_3NO_2$: Cl, 55.25. Found: Cl, 54.88.

2,2,2-Trichloroacetamide (31) was prepared by treating the acid chloride with concentrated NH_4OH: 76% yield; mp 141–142.5° (lit.[20] mp 137°).

Typical Procedure for the Monochlorination of Carbamates and Carboxamides. Preparation of Ethyl *N*-Chlorocarbamate (1). To 35.6 g (400 mmol) of ethyl carbamate in a 2-l. conical flask cooled in an ice bath was added 545 ml of yellow NaOCl solution (0.73 mmol/ml, 398 mmol). The mixture was stirred until it became colorless (15 min). Methylene chloride (300 ml) was added. Then 241 ml (482 mequiv) of 2 *N* H_2SO_4 was added dropwise with vigorous stirring. The addition took 2 hr. The organic phase was decanted and the aqueous layer was extracted with methylene chloride (4 × 100 ml). The combined extracts were dried (Na_2SO_4) and the solvent was removed on the rotatory evaporator at *ca.* 25° to yield 49.0 g of **1** as a pale yellow oil which crystallized upon cooling (see Table I): ir (CCl_4) 3400, 3300 (broad), 1770, 1730, 1700, 1380, 1330, 1310, 1200, and 1060 cm^{-1}; nmr

($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 4.28 (q, J = 7 Hz, 2 H), and 6.63 (broad s, 1 H).

The other *N*-chloroamides listed in Table I were prepared in the same way but on a smaller scale (from 10 to 100 mmol), the excess of amide varying from 1 to 2%. With amides very insoluble in water, a larger reaction time was needed (up to 30 min) with a few milliliters of methylene chloride being added to speed up the reaction. When working on a 10–40-mmol scale, acidifications were carried out with 1 *N* H_2SO_4. Because of the higher solubility of *N*-chlorocarboxamides in water, four to ten extractions with methylene chloride were performed. The ir spectra (CCl_4) of the *N*-chlorocarbamates **2–6** are quite similar to that of ethyl *N*-chlorocarbamate (**1**) and they all show a band in the following regions: 3400 (free NH), 3200–3180 (broad, associated NH), 1770 (C=O), 1740–1730 (C=O), 1710–1700 (C=O), 1410–1380, 1350–1330, 1200 (ester), and 1080–1000 cm^{-1} (ester).

Typical Procedure for the Monobromination of Carbamates and Carboxamides. Preparation of Ethyl *N*-Bromocarbamate (17). To 4.43 g (43 mmol) of NaBr was added 53.4 ml of NaOCl solution (0.75 mmol/ml, 40 mmol). The mixture was stirred for 15 min at room temperature. The deep yellow hypobromite solution was cooled in an ice bath and 3.60 g (40.4 mmol) of ethyl carbamate was added. The reaction mixture was stirred until it became pale yellow (almost colorless). Methylene chloride (50 ml) was added followed by the dropwise addition of 41 ml (47 mequiv) of 1.15 *N* H_2SO_4 with vigorous stirring. The addition took 1.5 hr. The reddish organic phase was decanted and the aqueous layer was extracted with methylene chloride (3 × 15 ml). The combined extracts were dried (Na_2SO_4) and the solvent was removed on the rotatory evaporator to yield 5.71 g of **17** as a yellow oil (see Table I): ir (CCl_4) 3400, 3200 (broad), 1720 (broad, strong), 1415, 1375, 1330, 1220, 1190 (shoulder), and 1065 cm^{-1}, and weak bands at 3500 and 1590 cm^{-1} due to the presence of ethyl carbamate; nmr (CCl_4) δ 1.28 (t, J = 7 Hz, carbamate CH_3) and 1.33 (t, J = 7 Hz, *N*-bromo- and *N,N*-dibromocarbamate CH_3), 4.17 (q, J = 7 Hz, carbamate CH_2) and 4.28 (q, J = 7 Hz, *N*-bromo- and *N,N*-dibromocarbamate CH_2), 5.41 (broad s, carbamate NH_2), and 6.55 (broad s, *N*-bromocarbamate NH) with the following relative integrations—7.7 (the two overlapping triplets), 5.0 (the two overlapping quadruplets), 1.0, and 1.6.

The other *N*-bromoamides listed in Table I were prepared in exactly the same way except that for water-insoluble amides, longer reaction time was needed (up to 30 min) for the reaction with NaOBr. The ir and nmr absorptions of the crude *N*-bromocarbamates **18** and **19** are given below.

Crude **18**: ir ($CHCl_3$) 3400, 3200 (broad), 1745 (broad, strong), 1390, 1325, 1230, 1185, 1110, and 1045, and weak bands at 3530 and 1585 cm^{-1} (nonbrominated carbamate); nmr (CCl_4) δ 4.75 (s, carbamate CH_2), 4.81 (s, *N*-bromo- and *N,N*-dibromocarbamate CH_2), 5.60 (broad s, carbamate NH_2), 6.40 (broad s, *N*-bromocarbamate NH) with a relative integration of 1.9:8.7:1.0:4.6.

Crude **19**: ir (CCl_4) 3400, 3240 (broad), 1720 (broad, strong), 1395, 1325, 1210, 1180 (shoulder), and 1050, and weaker bands at 3500 and 1590 cm^{-1} (nonbrominated carbamate); nmr (CCl_4) δ 5.05 (s, carbamate CH_2), 5.85 (s, *N*-bromocarbamate CH_2), 5.35 (broad s, carbamate NH_2), 6.48 (broad s, *N*-bromocarbamate NH), 7.30 and 7.33 (s, aromatic H of the carbamate and the *N*-bromo derivative) with a relative integration of 1.0:2.3:1.1:1.2:7.7.

Registry No.—**1**, 16844-21-6; **2**, 52175-97-0; **3**, 52175-98-1; **4**, 30830-84-3; **5**, 30830-85-4; **6**, 30830-47-8; **7**, 52175-99-2; **8**, 598-49-2; **9**, 36448-95-0; **10**, 52176-00-8; **11**, 35070-76-9; **12**, 35070-77-0; **13**, 35077-08-8; **14**, 35077-09-9; **15**, 35077-10-2; **16**, 52176-01-9; **17**, 52176-02-0; **18**, 52176-03-1; **19**, 52176-04-2; **20**, 3699-17-0; **21**, 3699-20-5; **22**, 52176-05-3; **23**, 52176-06-4; **24**, 35077-11-3; **25**, 36015-63-1; **26**, 52259-82-2; **27**, 35077-12-4; **28**, 359-45-5; **29**, 627-12-3; **30**, 1616-88-2; **31**, 2114-18-3; **32**, 107-69-7; sodium hypochlorite 7681-52-9; sodium hypobromite, 13824-96-9.

Supplementary Material Available. Characteristic ir absorptions (position of the NH and C=O bands) of the *N*-chlorocarboxamides **9–16** and of the *N*-bromocarboxamides **20–26**, and the nmr absorptions of these *N*-haloamides and of the *N*-chlorocarbamates **2–6** will appear in Table II (ir) and Table III (nmr) following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3136.

References and Notes

(1) (a) Supported by a grant from the National Research Council of Canada; (b) Arts Council of Canada Predoctoral Fellow, 1969–1971; (c) NRCC Postdoctoral Fellow, 1968–1970; (d) France-Quebec Predoctoral Fellow, 1970–1972.
(2) (a) J. Lessard and J. M. Paton, *Tetrahedron Lett.*, 4883 (1970); (b) J. Lessard and H. Driguez, *ibid.*, 4887 (1970); (c) H. Driguez and J. Lessard, unpublished work.
(3) D. Touchard and J. Lessard, *Tetrahedron Lett.*, 4425 (1971); 3827 (1973).
(4) S. C. Czapf, H. Gottieb, G. F. Whitfield, and D. Swern, *J. Org. Chem.*, **38**, 2555 (1973).
(5) Sodium hypobromite was prepared from sodium hypochlorite and sodium bromide.[6]
(6) A. Kergomard, *Bull. Soc. Chim. Fr.*, 2360 (1961).
(7) As shown by Swern and coworkers,[4] the equilibrium of the disproportionation reaction of the *N*-chlorocarbamates seems to lie completely toward the monochloro derivative at ambient temperature. Indeed, we could not detect the presence of any nonchlorinated carbamate in the ir (no bands at 3530 and 1585 cm^{-1}) and nmr spectra of *N*-chlorocarbamates of purity ≥99% (iodometric analysis and acid value determination).
(8) A. L. J. Beckwith and J. E. Goodrich, *Aust. J. Chem.*, **18**, 747 (1965).
(9) T. Imamoto, Y. Tsuno, and Y. Yukawa, *Bull. Chem. Soc. Jap.*, **44**, 1632 (1971), and references cited therein.
(10) J. D. Park, H. J. Gerjovich, W. R. Lycan, and J. R. Lacker, *J. Amer. Chem. Soc.*, **74**, 2189 (1952).
(11) T. R. Beebe and J. W. Wolfe, *J. Org. Chem.*, **35**, 2056 (1970).
(12) Wolfe and Awang[13] have reported that *N*-bromoacetamide, when irradiated (photoflood lamp) in refluxing carbon tetrachloride and in the presence of an olefin, undergoes disproportionation. The *N,N*-dibromoacetamide formed reacts rapidly with the olefin to give a β-bromo-*N*-bromoacetimidate.
(13) S. Wolfe and D. V. C. Awang, *Can. J. Chem.*, **49**, 1384 (1971).
(14) See paragraph at end of paper regarding supplementary material.
(15) Commercial hypochlorite solutions from other sources were also used but were found to give less satisfactory results.
(16) B. Loev and M. F. Kormendy, *J. Org. Chem.*, **28**, 3421 (1963).
(17) W. M. Kraft and R. M. Herbst, *J. Org. Chem.*, **10**, 483 (1945).
(18) H. G. Ashburn, A. R. Collett, and C. L. Lazzell, *J. Amer. Chem. Soc.*, **60**, 2934 (1938).
(19) J. I. Jones, *J. Chem. Soc.*, 2735 (1957).
(20) L. McMaster and F. B. Langreck, *J. Amer. Chem. Soc.*, **39**, 108 (1917).

Liquid Crystals. V. Molecular Structural Effects on the Mesomorphism of Phenylene Esters[1]

D. W. Bristol and J. P. Schroeder*

Department of Chemistry, The University of North Carolina at Greensboro, Greensboro, North Carolina 27412

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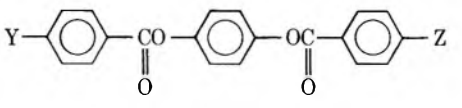
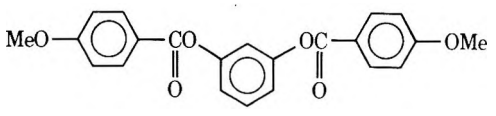
In an earlier paper,[1b] we reported the effects on the mesomorphism (liquid crystallinity)[2-4] of terminally substituted *p*-phenylene dibenzoates (**1**) caused by changing the



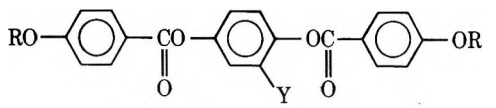
1

end groups. It was shown that this molecular system has a marked tendency to exhibit nematic mesomorphism, which survives major variations of Y and Z. Since then, we have investigated the effects of more drastic alterations in structure: halogen and methyl substituents on the central phenylene ring, methyl substituents in the 3 and 5 positions of the benzoyl groups, replacement of the central *p*-phenylene with *m*-phenylene and of benzoyl with cinnamyl, and the combination of central chloro substitution with dissimilar acyl groups.

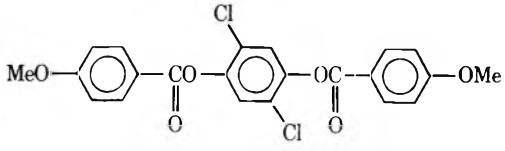
The esters that were prepared have the following structures.



2



3a, R = Me; Y = Me
b, R = Me; Y = Cl
c, R = Me; Y = Br
d, R = n-C_6H_{13}; Y = Cl



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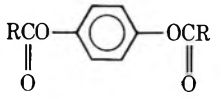
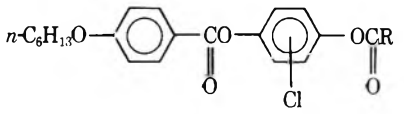
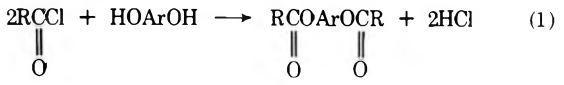


5a, R = 3,4-$Me_2C_6H_3$
b, R = 3,5-$Me_2C_6H_3$
c, R = 4-$MeOC_6H_4CH{=}CH$

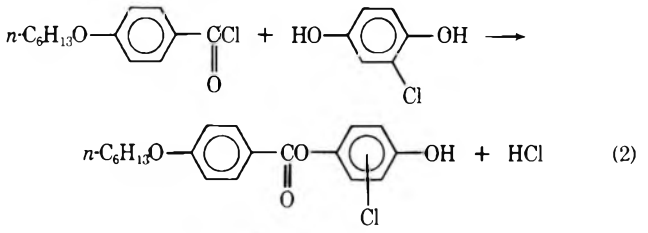


6a, R = 4-n-$C_4H_9C_6H_4$
b, R = 4-n-$C_8H_{17}OC_6H_4$
c, R = 3,5-$Me_2C_6H_3$
d, R = 4-$MeOC_6H_4CH{=}CH$

Esters with two identical acyl groups (**2–5**) were synthesized by the process shown in eq 1, and esters of type **6** by the process shown in eq 2 and 3.



(1)



(2)

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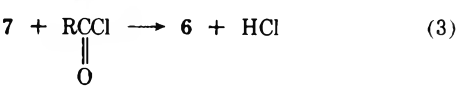


(3)

Experimental Section

Substituted Benzoic and Cinnamic Acids. 4-n-Hexyloxy-, 4-n-octyloxy- (Frinton), 3,4-dimethyl- (Eastman), and 3,5-dimethylbenzoic acid (Aldrich) and *trans*-4-methoxycinnamic acid (Aldrich) were purchased. 4-n-Butylbenzoic acid was prepared by hydrolysis of the corresponding nitrile with NaOH in EtOH–H_2O. After recrystallization from EtOH–H_2O, the product had mp 98°, N–I point[5] 112° (lit. 98°, 112°,[6] 102°, 112° [7]). 4-n-Butylbenzonitrile was obtained by the Sandmeyer method[8] from 4-n-butylaniline (Eastman).

Acyl Chlorides. 4-Anisoyl chloride was a commercial product (Eastman). The others were made from the corresponding acids by treatment with $SOCl_2$ at reflux in the presence of pyridine. Excess $SOCl_2$ was distilled to give the acid chlorides as residues.

Diphenols. Hydroquinone (Matheson Coleman and Bell), resorcinol (Fisher), and methyl-, chloro-, and 2,5-dichlorohydroquinone (Eastman) were purchased. Bromohydroquinone, mp 112° (lit.[9] mp 111°), was synthesized by bromination of hydroquinone with dioxane dibromide[9] when attempts to purify a commercial material (Eastman, practical grade) were unsuccessful.

2- and 3-Chloro-4-hydroxyphenyl 4-n-Hexyloxybenzoate (7). A mixture of these isomers was prepared by overnight reaction of chlorohydroquinone (0.10 mol) and 4-n-hexyloxybenzoyl chloride (0.017 mol) in 90 ml of dry pyridine at room temperature. The resulting mixture was poured into 300 ml of 2 N aqueous HCl. An oil separated which was washed with aqueous $NaHCO_3$ and then H_2O. Extraction with 95% EtOH left by-product **3d** as the residue. Crude **7** was recovered from the extract by precipitation with H_2O. The precipitate was dissolved in ether, and the solution was washed with aqueous $NaHCO_3$ and treated with Norit. Recrystallization from 90–120° petroleum ether gave a 53% yield of **7**, mp 109–112°. *Anal.* Calcd for $C_{19}H_{21}O_4Cl$: C, 65.41; H, 6.08. Found: C, 65.43; H, 5.94.

Phenylene Diesters. Typically, for the preparation of type **2–5** esters, 1 molar equiv of diphenol and 4 molar equiv of acyl chloride were allowed to react overnight in dry pyridine at room temperature. The mixture was then poured into a large volume of H_2O. The precipitate was removed by filtration, washed with H_2O and aqueous $NaHCO_3$, and recrystallized from a suitable solvent after treatment with Norit. The procedure for preparing **6a–d** was generally similar, using **7** instead of a diphenol. The exception was the reaction of **7** and 4-methoxycinnamyl chloride, which gave a highly colored product by this method, and so was run in benzene rather than pyridine solution. Excess acyl chloride can be recovered (as the acid) by acidification of the alkaline filtrate and/or aqueous $NaHCO_3$ wash liquor with hydrochloric acid.

The results are summarized in Table I.

Table I
Phenylene Diesters[a]

Compd[b]	Recrystn solvent	Yield, %	Melting range, °C	N–I point, °C
2	EtOH	92	137–138	*c*
3a	EtOH–acetone	96	169–170	250[d]
3b	EtOAc	97	165–166.5	254[d]
3c	EtOAc	94	162.5–164, 168.5–170[e]	249.5[d]
3d	EtOH–dioxane	47	89–90	169.5
4	Dioxane	94	234.5–236	(215)[f]
5a	Acetone	16	207–208	*c*
5b	EtOH	73	156–158.5	*c*
	Cyclohexane		170.5–172.5[e]	
5c	Dioxane	64	209–214	>337[g]
6a	Pentane	8	70–78	158
6b	Hexane	52	75–77	161.5
6c	MeOH	30	96.5–102.5	*c*
6d	90–120° petroleum ether	49	119–167	238

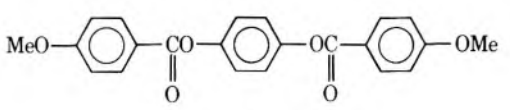
[a] Satisfactory analytical data (±0.4% for C and H) were reported for all compounds in the table. [b] **5c** and **6a–d** are believed to be mixtures of isomers. [c] Not mesomorphic. [d] These compounds exhibit monotropic nematic–smectic transitions at 126 (**3a**), 127.5 (**3b**), and 130° (**3c**). [e] Polymorphic. [f] Monotropic transition. [g] Decomposition begins at this temperature.

Apparatus. Transition temperatures were determined with a Reichert Thermopan polarizing microscope equipped with a Kofler micro hot stage. The instrument was calibrated against pure compounds having known melting points. Some of the transitions were checked by means of a Perkin-Elmer differential scanning calorimeter, Model DSC-1B.

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

Results and Discussion

As mentioned above, system **1** shows a remarkable propensity toward nematic mesomorphism.[1b] Among esters of type **1**, the di-*p*-anisoate (**8**) displays one of the most stable



8

nematic mesophases (nematic range, 222–300°)[10] and, therefore, in studying the effects of altering the central phenylene ring on the mesomorphism of system **1**, **8** was selected as the reference compound.

The molecular structural criteria for mesomorphism are linearity, rigidity, and polarity. In **2**, the central *p*-phenylene of **8** is replaced by *m*-phenylene. No significant changes in rigidity or polarity should result and, while less linear, the molecule **2** is capable of adopting a configuration that must certainly be considered rod-shaped. Yet **2** melts 84° below **8** and is not liquid crystalline, so that the N–I point has been depressed at least 162°. By contrast, replacement of the central *p*-phenylene in **8** by 1,4-bicyclo[2.2.2]octylene and *trans*-1,4-cyclohexylene only lowers the melting point 37 and 25°, and the N–I point 31 and 105°, respectively.[11] The alicyclic units are less polarizable than phenylene and cyclohexylene is less rigid, but they preserve linearity. These comparisons constitute a striking example of the effects of molecular symmetry on melting point and of molecular linearity on mesomorphism.

Substituents on the central *p*-phenylene were also explored. Arora, *et al.*,[12] showed that a methyl group in this position lowers both the melting and N–I point about 40° in the *n*-hexyloxy and higher homologs of **8**. Our results for a similarly placed chloro substituent in the *n*-hexyloxy (**3d**) and *n*-hexyloxy–*n*-octyloxy (**6b**) homologs are much the same. For a methyl (**3a**), chloro (**3b**), or bromo (**3c**) group in **8** itself, the lowering of the transition temperatures is greater (about 50°). Two chloro groups in the 2 and 5 positions of the central ring of **8** (**4**) lower the N–I point almost twice as much as one (85 *vs.* 46°), indicating that the effect is additive.[3] However, the melting point of **4** is 14° higher than that of **8**, probably because of increased polarity and molecular weight with little sacrifice in molecular symmetry.

The lower thermal stability of the nematic mesophase produced by substituents on the central ring seems to be a steric effect, the bulky groups preventing close lateral approach of adjoining parallel molecules and thereby diminishing intermolecular attractive forces.[3] The same effect should also lower smectic mesophase stability and, indeed, Arora, *et al.*,[12] found this to be true. It is well known that smectic behavior is usually enhanced by long *n*-alkyl end groups.[3] For the *n*-hexyloxy and higher homologs of **8**, these workers first encountered smectic mesomorphism in the heptyloxy ester (N–Sm point 110°) on ascending the series. For the analogous esters with a methyl on the central ring, a smectic mesophase did not appear until the undecyloxy compound (N–Sm point 74°). The situation for chloro substitution is similar. The ester **1** (Y = *n*-$C_6H_{13}O$, Z = *n*-$C_8H_{17}O$)[13] is smectic (Sm–N point 107°) whereas its chloro-substituted counterpart (**6b**), mp 77°, is not. Furthermore, the *n*-hexyloxy homolog with the central chloro group (**3d**) is not smectic even when supercooled to 54°. Therefore, our observation of smectic mesomorphism, and at fairly high temperatures (126–130°), in the *methoxy* esters with methyl (**3a**), chloro (**3b**), and bromo (**3c**) groups in the central *p*-phenylene ring came as a surprise.

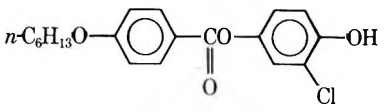
We can only speculate as to the reason for this unusual behavior. Compound **8** and its homologs are compatible structurally with smectic mesomorphism, having the strong dipoles crosswise to the molecular long axis associated with ester linkages, which are often present in smectic compounds.[14] In **3a–c**, these are buttressed by the additional crosswise dipole produced by the substituent on the central ring. Thus, although unexpected, the appearance of a smectic mesophase is not illogical. *n*-Alkyl end groups of intermediate length would further enhance lateral attraction if forced into parallel, extended configurations by close approach of adjacent molecules, but this is hindered by the bulky substituent. In fact, such alkyl groups seem to exert a deleterious effect on smectic mesomorphism, perhaps by assuming random configurations and thus decreasing molecular linearity. For terminal *n*-alkyl chains of great length, the natural extended configuration (as in linear polyethylene) appears to be reachieved and a smectic mesophase is again observed. If this view is correct, the N–Sm point should decrease at first as the homologous series starting with **3a–c** is ascended, then pass through a minimum value, and finally rise again. We intend to prepare the presently missing members of the three series in order to test the hypothesis.

Turning next to variations of the acyl groups in system **1**, in **5a** these are 3,4-dimethylbenzoyl, so that there are two terminal and two lateral methyl substituents. It is convenient to compare nonmesomorphic **5a**, mp 208°, and the corresponding ester without the lateral methyls (**1**, Y = Z = Me), mp 231.5°, N–I point 236°.[1b] Introduction of the side groups lowers the melting point 23.5° and the N–I point at least 28°. In **5b**, the acyl groups are 3,5-dimethylbenzoyl; *i.e.*, there are four lateral methyl substituents. This compound exhibits polymorphism, melting at 158.5° when recrystallized from ethanol and at 172.5° when recrystallized from cyclohexane.[15] It is not mesomorphic so, relative to **1** (Y = Z = Me), the N–I point is lower by at least 77.5°. The decrease in transition temperatures with increasing lateral substitution exemplified by **5a** and **5b** is in accord with generally accepted theory. Bulky side groups inhibit close approach of neighboring molecules and, therefore, diminish intermolecular attraction. In addition, they make the molecule less rod-shaped. In **5c**, mp 209–214°, N–I point >337°, the acyl groups are 4-methoxycinnamyl. This compound is best compared with **8**, from which it differs by insertion of CH=CH between the benzene ring and carbonyl in the acyl groups. The resulting increased molecular length and polarizability are consistent with the significant increase in the N–I point. For the same reasons, one would expect a higher melting point also. The fact that **5c** melts 8° lower than **8**, and over a temperature range, leads us to believe that it is a mixture of geometric isomers, three of which (trans,trans, cis,trans, and cis,cis) are possible. *trans*-4-Methoxycinnamic acid was used in preparing **5c**, but some isomerization could have occurred during the synthesis. Any cis geometry would decrease molecular linearity and, therefore, nematic mesophase stability. In consideration of the high N–I point, it appears that **5c** is mainly the trans,trans isomer.

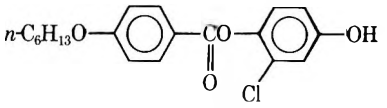
The remaining materials (**6a–d**) represent attempts to prepare low-melting nematic esters of type **1**. Four factors known to contribute to low melting points were employed: mixtures, molecular dissymmetry, a bulky lateral substituent, and a long chain *n*-alkoxy end group. In each instance, the starting material was the phenolic ester **7**, prepared by nucleophilic displacement of chlorine from *p*-*n*-hexyloxybenzoyl chloride by chlorohydroquinone (eq 2). Either of the OH groups in the latter may serve as the nucleophilic center, so that two isomeric products (**7a** and **7b**) are possible. The generally broad melting ranges of **6a–d** suggest that **7** is a mixture of **7a** and **7b**, and that this position isomerism is carried forward into the final products which, as a result, are mixtures. For **6d**, there is the additional

possibility of cis–trans isomerism. The ester molecules are dissymmetric because of the chloro substituent and the two different acyl groups.

Three of the four materials are nematic. The exception is **6c**, demonstrating again the powerful deleterious effect of bulky lateral substituents on mesomorphism. The high melting and N–I points of **6d**, although it is obviously a mixture, suggest that the main components are the *trans*-4-methoxycinnamates of **7a** and **7b**. **6a** and **6b** are the low-

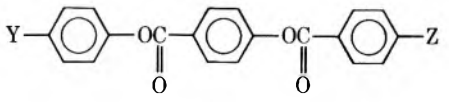


7a



7b

est melting examples of type 1 esters to date. This is consistent with their being mixtures and with their structures. The combination of a chloro substituent on the central *p*-phenylene ring with terminal *n*-alkyl or *n*-alkoxy groups in a very closely related system (**9**) has been shown[16] to result



9

in low-melting (39–70°) (nematic) compounds. The relatively low melting point of **3d** is also consistent with this.

Acknowledgment. We wish to thank Stephen A. Haut for suggesting the preparation of compound **2**.

Registry No.—**2**, 51933-64-3; **3a**, 51933-65-4; **3b**, 51933-66-5; **3c**, 51933-67-6; **3d**, 51933-68-7; **4**, 51933-69-8; **5a**, 51933-70-1; **5b**, 51933-71-2; **5c**, 51933-72-3; **6a**, 52003-48-2; **6b**, 52003-49-3; **6c**, 52003-50-6; **6d**, 52124-32-0; **7**, 52003-51-7.

References and Notes

(1) (a) This work was supported by a grant from the Research Council of the University of North Carolina at Greensboro. (b) Previous paper in this series: J. P. Schroeder and D. W. Bristol, *J. Org. Chem.*, **38**, 3160 (1973).
(2) G. H. Brown and W. G. Shaw, *Chem. Rev.*, **57**, 1049 (1957).
(3) G. W. Gray, "Molecular Structure and the Properties of Liquid Crystals," Academic Press, New York, N. Y., 1962.
(4) A. Saupe, *Angew. Chem., Int. Ed. Engl.*, **7**, 97 (1968).
(5) Nematic–isotropic transition temperature. The following abbreviations are used in this note: N = nematic, Sm = smectic, and I = isotropic.
(6) R. Steinsträsser, *Z. Naturforsch. B*, **27**, 774 (1972).
(7) W. R. Young, I. Haller, and D. C. Green, *J. Org. Chem.*, **37**, 3707 (1972).
(8) H. T. Clarke and R. R. Read, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 514.
(9) L. A. Yanovskaya, A. P. Terentyev, and L. I. Belenky, *Zh. Obshch. Khim.*, **22**, 1594 (1952); *J. Gen. Chem. USSR*, **22**, 1635 (1952).
(10) M. J. S. Dewar and J. P. Schroeder, *J. Org. Chem.*, **30**, 2296 (1965).
(11) M. J. S. Dewar and R. S. Goldberg, *J. Amer. Chem. Soc.*, **92**, 1582 (1970).
(12) S. L. Arora, J. L. Fergason, and T. R. Taylor, *J. Org. Chem.*, **35**, 4055 (1970).
(13) S. A. Haut, D. C. Schroeder, and J. P. Schroeder, *J. Org. Chem.*, **37**, 1425 (1972).
(14) Reference 3, pp 166 and 188.
(15) Ester **3c** is also polymorphic. Two distinct fusions were seen in the melting point determination (Table I), and a DSC trace gave peaks at 163 and 172°. Cooling and reheating the sample in the DSC gave mainly a peak at 177.5°, which was also the result when the compound was recrystallized from ethanol rather than ethyl acetate.
(16) J. P. VanMeter and B. H. Klanderman, *J. Amer. Chem. Soc.*, **95**, 626 (1973).

A Reexamination of the Effect of α- and β-Methyl Substitution on the Esterification Rates of Saturated Aliphatic Acids

Paul J. Sniegoski

Naval Research Laboratory, Washington, D. C. 20375

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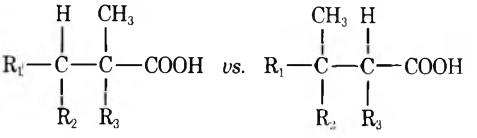
From an examination of his collection of data concerning the hydrogen chloride catalyzed esterification rates in methanol of various aliphatic acids, Newman concluded "... substitution of methyl groups for hydrogen causes a greater decrease in rate when at the beta-carbon than when at the alpha- or gamma-carbon."[1] Essentially the same conclusion was reached by Taft, "In each case methyl substitution is more effective in the beta than in the alpha position,"[2] and by Schulte and Kirschner, "... the influence of the methyl group in the beta position is somewhat greater than in the alpha position."[3] This general conclusion has been widely accepted.[4]

However, by looking at the effect of α- and β-methyl substitution in a much simpler scheme, one not generally carried out by the authors cited, the opposite effect is observed, namely that an α-methyl substitution decreases the rate *more* than a β-methyl substitution. This simple and direct scheme consists of the comparison of the rates of sets of two isomeric acids, differing only in the α or β placement of a methyl group.



α-methyl acid vs. β-methyl acid

The results from ten such sets are given in Table I. Five of the sets of data are from Newman's collection; the remainder were obtained from gas chromatographic analysis of partly esterified mixtures of acids. Details of the gas chromatographic method used for sets 8 and 9 are given in the experimental section. Data in Table II show that this method is capable of considerable precision.

Because of branching, an α-methyl acid may have two β-methyl acids for comparison of rates. In all cases except example number 10 of Table I, the β-methyl acid of the set esterifies faster than the α-methyl isomer. The average for the k_β/k_α ratios in examples 1–9 is 1.8 ± 0.5. Example number 10 consists of a set of much more sterically hindered acids than the others and appears to be the only case where Newman made use of the comparison of such isomers to demonstrate his conclusion. No actual numerical ratio was established by Newman between the rates of these two acids since the rate for the β-methyl acid was considered to be too slow for measurement.

Yufit has apparently taken Newman's data (without crediting him) and developed an empirical method for calculating the esterification rates of the aliphatic acids from their structures.[7] Unfortunately, his calculations for the various acids do not always seem to follow his method as stated; however, for the simple case of placing a methyl group in the α or β position of a normal acid, it can be shown that the general prediction is that the β-methyl acid will esterify (presumably at 40°) ~1.4 times as fast as the α-methyl acid. Thus, from exactly the same body of data entirely different conclusions were reached by the methods of Yufit and Newman.

From an examination of the data in Table I, it seems rea-

Table I

Relative Esterification Rates in Methanol of α-Methyl- and β-Methyl-Substituted Aliphatic Acids

No.	α-Methyl acid, $(R_1)(R_2)CHC(R_3)(CH_3)COOH$	β-Methyl acid, $(R_1)(R_2)(CH_3)CCH(R_3)COOH$	$k\beta/k\alpha$	Temp, °C	Ref
1	$(CH_3)_2CHCOOH$	$CH_3CH_2CH_2COOH$	1.5	40	1
2	$CH_3CH_2CH(CH_3)COOH$	$CH_3CH(CH_3)CH_2COOH$	1.2 (1.1)	40	1 (3)
3	$(CH_3)_3CCOOH$	$CH_3CH_2CH(CH_3)COOH$	2.7	40	1
4	$CH_3CH_2CH_2CH(CH_3)COOH$	$CH_3CH_2CH(CH_3)CH_2COOH$	1.2	65	5
5	$CH_3CH_2C(CH_3)_2COOH$	$CH_3CH(CH_3)CH(CH_3)COOH$	2.3	65	5
6	$CH_3CH_2C(CH_3)_2COOH$	$CH_3CH_2CH(C_2H_5)COOH$	2.3	65	5
7	$(CH_3)_2CHCH(CH_3)COOH$	$(CH_3)_3CCH_2COOH$	1.5 (1.6)	15–20 (35)	1 (5)
8	$CH_3CH_2CH_2CH_2C(CH_3)_2COOH$	$CH_3CH_2CH_2CH_2CH(C_2H_5)COOH$	1.6	50	This report
9	$(CH_3)_2CHCH_2C(CH_3)_2COOH$	$(CH_3)_2CHCH_2CH(C_2H_5)COOH$	2.2	50	This report
10	$(CH_3)_3CC(CH_3)_2COOH$	$(CH_3)_3CCH(C_2H_5)COOH$	<1[6]	40	1

Table II
Determination of Relative Esterification Rates in Methanol at 50° of α-Methyl- and β-Methyl-Substituted Aliphatic Acids

Fraction remaining after partial esterification		
α-Methyl acid (A) 2,2,4-Trimethylpentanoic acid[a]	β-Methyl acid (B) 2-Ethyl-4-methylpentanoic acid[b]	Log B/log A
0.6622	0.4150	2.13
0.6413	0.4014	2.05
0.5428	0.2589	2.21
0.5503	0.2621	2.24
0.4704	0.1775	2.29
0.4553	0.1731	2.23
2,2-Dimethylhexanoic acid[c]	2-Ethylhexanoic acid[d]	Log B/log A
0.8118	0.7208	1.57
0.6714	0.5319	1.58
0.5054	0.3298	1.63
0.3272	0.1750	1.56
0.1791	0.0731	1.52

[a] Registry number, 866-72-8. [b] Registry number, 108-81-6. [c] Registry number, 813-72-9. [d] Registry number, 149-57-5.

sonable to put forth the following generalization: a β-methyl-substituted saturated aliphatic acid esterifies with methanol at a greater rate (~1.8 times as fast at 40°) than the corresponding α-methyl acid.

Although the above statement deals only with certain isomeric pairs of acids, it certainly presents a multitude of "exceptions" to the generally accepted conclusion that a methyl substitution at the β carbon is more effective in reducing the esterification rate than a methyl substitution at the α carbon. How the conclusion developed in this present report can be employed to predict more satisfactorily the effect of structure on esterification rates will be the topic of a forthcoming paper.

Experimental Section

Materials. Purity of the acids was indicated by the neutralization equivalent (144.2 calcd) and the per cent area by glc under the conditions described in the next section.

2-Ethylhexanoic acid, neut equiv 144.6, glc per cent area 99.8, was obtained from Baker Chemical Co.

2-Ethyl-4-methylpentanoic acid, neut equiv 144.8, glc per cent area 99.1, was obtained from Pfaltz and Bauer.

2,2-Dimethylhexanoic acid, neut equiv 145.1, glc per cent area 95.7, was prepared by alkaline permanganate oxidation of 2,2-dimethyl-1-hexanol obtained from K & K Laboratories.

2,2,4-Trimethylpentanoic acid, neut equiv 146.5, glc per cent area 98.6, was prepared by alkaline permanganate oxidation of 2,2,4-trimethyl-1-pentanol obtained from Pfaltz and Bauer.

Methyl myristate, glc per cent area 99.8, was obtained from Lachat Chemicals Inc.

Gas–Liquid Chromatography. Chromatography was carried out with a Beckman GC 4 chromatograph equipped with a flame ionization detector which was interfaced with a Perkin-Elmer PEP-1 data processer. The column was 6 ft by ⅛ in. stainless steel packed with 20% diethylene glycol adipate polyester and 3% phosphoric acid on 60/80 mesh Gas-Chrom P. Column temperature was 150°, inlet temperature was 200°, and helium flow was 25 cc/min.

Determination of the Relative Esterification Rates. The reaction mixture was composed of 20 ml of methyl alcohol, 2 drops of each of the two acids whose esterification rates are to be determined, and 2 drops of methyl myristate, the internal standard. It is, of course, necessary that all three components are adequately resolved by the chromatographic method. Six drops of concentrated hydrochloric acid was added; the mixture was divided up into a number of small screw-cap tubes and heated in an aluminum block at 50 ± 0.5°. Samples were analyzed at various times over a 4-hr heating period. Readouts from the data processer were given as fraction remaining of each of the acids. The relative esterification rate was calculated from the equation

$$\frac{k_{\beta\text{-methyl acid}}}{k_{\alpha\text{-methyl acid}}} = \frac{\log \text{fraction remaining of } \beta\text{-methyl acid}}{\log \text{fraction remaining of } \alpha\text{-methyl acid}}$$

Readouts and the calculated relative esterification rates are given in Table II.

References and Notes

(1) M. S. Newman in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, pp 204–212.
(2) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 600.
(3) K. E. Schulte and J. Kirschner, *Fette Seifen*, **5**, 267 (1951).
(4) (a) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp 322–324; (b) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold, New York, N. Y., 1961, pp 374–376; (c) E. K. Euranto in "The Chemistry of Carboxylic Acids and Esters," S. Patai, Ed., Interscience, New York, N. Y., 1969, pp 556, 557; (d) C. A. Buehler and D. E. Fearson, "Survey or Organic Synthesis," Wiley-Interscience, New York, N. Y., 1970, p 804.
(5) P. J. Sniegoski, *J. Chrom. Sci.*, **10**, 644 (1972).
(6) The rate for the α-methyl acid was the smallest one measured in Newman's series; the rate for the β-methyl acid was "too small for measurement." Therefore, (too small for measurement)/(any measurement) is less than 1.
(7) S. S. Yufit; *Izv. Akad. Nauk, Otd. Khim. Nauk*, **10**, 1784 (1962); English translation in *Bull. Acad. Sci. USSR Div. Chem. Sci.*, **7**, 1662 (1962).

Absence of Catalysis of Salicylate Ester Hydrolysis by Hexadecyltrimethylammonium Bromide Micelles

Linda J. Magid* and John W. Larsen

Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37916

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Rate enhancements by cationic micelles have been observed in the base-catalyzed hydrolysis of several carboxylic esters having good leaving groups.[1] With simple alkyl esters rate retardations have been observed; they have been

Table I
Hydrolysis of Methyl and Hexyl Salicylate at 25° [a]

[Ester], M	[CTAB], M	pH	$k \times 10^5$, sec^{-1}
10^{-3} M methyl salicylate		9.2[b]	1.59 ± 0.02
		9.2[b]	1.69 ± 0.03
	0.00497	9.2[b]	1.12 ± 0.05
	0.00500	9.2[b]	0.605 ± 0.036
	0.0505	9.2[b]	0.281 ± 0.009
		10.0[c]	1.95 ± 0.09
		10.0[c]	3.24 ± 0.09
		10.0[c]	1.88 ± 0.09
		10.0[c]	3.66 ± 0.15
	0.00500	10.0[c]	1.67 ± 0.05
	0.00500	10.0[c]	2.60 ± 0.34
		10.25[d]	1.69 ± 0.09
		10.25[d]	5.49 ± 0.08
		10.25[d]	4.94 ± 0.48
	0.00501	10.25[d]	2.16 ± 0.09
	0.00497	10.25[d]	2.20 ± 0.12
	0.00501	10.25[d]	2.40 ± 0.05
10^{-3} M hexyl salicylate	0.00503	9.2[b]	0.132 ± 0.005
	0.00111	10.0[c]	0.143 ± 0.006
	0.00348	10.0[c]	0.206 ± 0.006
	0.00454	10.0[c]	0.221 ± 0.004
	0.00500	10.0[c]	0.192 ± 0.004
	0.00551	10.0[c]	0.237 ± 0.002
	0.00654	10.0[c]	0.188 ± 0.008
	0.01000	10.0[c]	0.187 ± 0.007
	0.00501	10.25[d]	0.226 ± 0.006

[a] All solutions contain 0.02 M NaCl. [b] 0.02 M borax buffer. [c] 0.02 M carbonate buffer, 50% base. [d] 0.03 M carbonate buffer, 75% base.

attributed to solubilization of the esters in the micellar core.[2] This explanation does not seem adequate; why are not the esters with good leaving groups also solubilized in the micellar core?

Phenols are known to be solubilized in the outer portions of both nonionic and ionic micelles;[3,4] since salicylate esters have a phenolic hydroxyl group, they are good candidates for this type of solubilization. As a result of our thermodynamic studies on the binding of organic solutes to micelles of hexadecyltrimethylammonium bromide (CTAB),[5] it occurred to us that hydrolysis of salicylate esters might be effectively catalyzed by CTAB. Methyl salicylate has a small negative enthalpy of transfer (ΔH_{trans}) from H_2O to 0.1 M CTAB solutions, but salicylic acid, one of its hydrolysis products, interacts very favorably with CTAB micelles ($\Delta H_{trans} = -9.25$ kcal/mol, $\Delta G_{trans} = -2.06$ kcal/mol). If this interaction were important in the rate-determining step for salicylate ester hydrolysis, a rate acceleration in the presence of CTAB could be expected.

Table I presents pseudo-first-order rate constants for the hydrolysis of methyl and hexyl salicylate in CTAB. Because of the low solubility of hexyl salicylate in water, rates for its hydrolysis in the absence of CTAB were not obtained. The collected data do not show good reproducibility, but they are of sufficient quality for our purposes. The poor reproducibility is thought to be a consequence of the colorimetric method's sensitivity to pH. Also salicylate esters may form complexes with boric acid.[6]

The presence of CTAB makes little if any difference in the rate of hydrolysis of the salicylate esters, indicating that the CTAB micelle's favorable interaction with salicylic acid is not felt in the rate-determining step.

We would like to suggest an explanation for the difference in sensitivity of esters with good compared to poor leaving groups to micellar catalysis. We will limit our discussion of good leaving groups to the *p*-nitrophenoxide ion, because *p*-nitrophenyl esters have been used so extensively[1] in work on micellar catalysis.

For alkaline hydrolysis of *p*-nitrophenyl esters formation (and reversion to reactants) of the tetrahedral intermediate is clearly rate determining. This is not true for simple alkyl esters. Since hydroxide ion is involved in this step, the effect of a positively charged micellar surface on its activity will be important; if the micellar surface facilitates OH^- attack (by some mechanism other than simple approximation of reactants) on esters, the *p*-nitrophenyl ester hydrolyses will be accelerated.

For simple alkyl esters, the availability of water or some other proton donor is important in the rate-determining step (expulsion of alcohol from the tetrahedral intermediate). This results in alkaline hydrolysis of these esters being less favorable at or near the micelle surface than in bulk solution. Lapinte, *et al.*,[7] has also observed rate retardations in CTAB solutions for reactions where water is involved as a proton donor; CTAB solutions are regarded as being similar to DMSO in this respect.

The explanation in the preceding paragraph assumes that expulsion of alkoxide ion from the tetrahedral intermediate in hydrolysis of simple alkyl esters does not occur. This is contrary to the work of Jencks[8] on tetrahedral addition compounds formed from the *N,O*-trimethylenephthalimidium cation and aliphatic alcohols. For salicylate esters water can also be involved in the formation of the tetrahedral intermediate, since these compounds are known to be subject to intramolecular general base catalysis.[9] If formation of the tetrahedral intermediate is in fact rate determining for the salicylate esters (as it is for *p*-nitrophenyl esters) the observed effect of CTAB on their hydrolysis can still be rationalized.

Experimental Section

Esters. Methyl salicylate (Fisher Scientific, U. S. P.) was used as received. *n*-Hexyl salicylate was prepared from salicylic acid and 1-hexanol using *p*-toluenesulfonic acid and *p*-toluenesulfonyl chloride as catalysts.[10] Following work-up, distillation at reduced pressure through a glass helices packed column removed most of the unreacted 1-hexanol. Two cuts, bp 90–93° (0.05 mm), contained about 88% ester (12% 1-hexanol) and were used in the kinetic studies.

Hexadecyltrimethylammonium Bromide (CTAB). The CTAB (City Chemical Corp.) was recrystallized from CCl_4, then dried *in vacuo* for at least 24 hr at 60°. Titration of the CTAB using $AgNO_3$ gave a molecular weight of 363 (actual 364.5); its cmc (bromide ion selective electrode) was 9.1×10^{-4} M.

Kinetic Studies. All buffer components were reagent grade; the water for the buffer solutions was boiled prior to use. The increase in salicylic acid concentration during the hydrolysis reactions (at 24.95 ± 0.06°) was followed by monitoring the absorbance of its $FeCl_3$ complex[11] at 532 nm using a Beckman DU spectrophotometer. The blank used contained $FeCl_3$ in acidic solution. The presence of CTAB did cause a decrease in extinction coefficient, but Beer's law still was obeyed. The A_∞ values were determined after 10 half-lives, and they are the average of at least two determinations. Some difficulty in obtaining consistent color development (formation of the complex) was encountered. This is thought to be due to the sensitivity of the salicylic acid–ferric ion reaction to the pH of the solution.

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Registry No.—Methyl salicylate, 119-36-8; hexyl salicylate, 6259-76-3; CTAB, 57-09-0.

References and Notes

(1) J. H. Fendler and E. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970), and references cited therein.
(2) (a) A. G. Mitchell, *J. Pharm. Pharmacol.*, **14**, 172 (1962); (b) *ibid.*, **15**, 165 (1963); (c) *ibid.*, **16**, 43 (1964); (d) E. Ullmann, K. Thoma, and R. Rombach, *Arch. Pharm. (Weinheim)*, **301**, 363 (1968); (e) H. Nogami, S. Awazu, and N. Nakajima, *Chem. Pharm. Bull.*, **10**, 503 (1962); (f) N. Nakajima, *Yakugaku Zasshi*, **81**, 1684 (1961).
(3) G. Némethy and A. Ray, *J. Phys. Chem.*, **77**, 64 (1973).
(4) L. J. Magid, Ph.D. Thesis, University of Tennessee, 1973.
(5) J. W. Larsen and L. J. Magid, *J. Phys. Chem.*, **78**, 834 (1974).
(6) (a) D. W. Tanner and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 6954 (1967); (b) B. Capon and B. C. Ghosh, *J. Chem. Soc. B*, 472 (1966).
(7) (a) C. LaPinte and P. Viout, *Tetrahedron Lett.*, 4221 (1972); (b) V. Gani and P. Viout, *ibid.*, 5241 (1972); (c) V. Gani and C. LaPinte, *ibid.*, 2775 (1973).
(8) (a) N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, **96**, 507 (1974); (b) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).
(9) (a) M. L. Bender, F. J. Kézdy, and B. Zerner, *J. Amer. Chem. Soc.*, **85**, 3017 (1963); (b) T. C. Bruice and D. W. Tanner, *J. Org. Chem.*, **30**, 1668 (1965); (c) G. M. Menger and J. A. Donohue, *J. Amer. Chem. Soc.*, **95**, 432 (1973); (d) C. R. Wasmuth and D. A. Copeland, *ibid.*, **95**, 3808 (1973).
(10) R. M. Gel'shtein and N. F. Krivosheeva, *Metody Poluch. Khim. Reaktivov Prep.*, **13**, 5 (1965); *Chem. Abstr.*, **65**, 5395*b* (1966).
(11) J. D. DeMarco and A. D. Marcus, *J. Pharm. Sci.*, **51**, 1010 (1962).

Dimethyl β-Ketoadipate

Barbara J. Whitlock and Howard W. Whitlock, Jr.*

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

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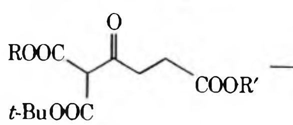
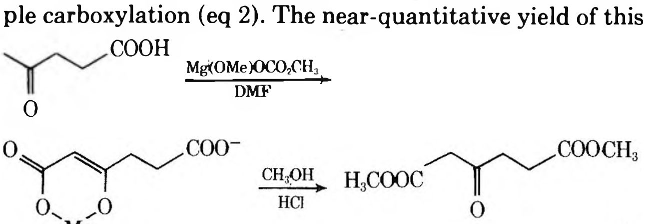
Several years ago there was reported a new and improved synthesis of several esters of the important biomolecule β-ketoadipic acid (I).[1] The starting materials employed were alkyl *tert*-butyl malonate and β-carboalkoxypropionyl chloride (eq 1). We report here an improvement

$ROOCCH_2COO\text{-}t\text{-}Bu + ClOCCH_2CH_2COOR' \longrightarrow$


→ I (1)

in the preparation that (a) avoids the problem of synthesis of the starting materials above and (b) employs cheap levulinic acid as starting material.

Carboxylation of levulinic acid by the procedure of Finkbeiner and Wagner[2] followed by Fischer esterification of the crude product affords a 92% isolated yield of dimethyl β-ketoadipate. There was no evidence for formation of the isomeric dimethyl acetylsuccinate or products from multiple carboxylation (eq 2). The near-quantitative yield of this


(2)

preparation requires use of a large (tenfold) excess of the carboxylating agent methylmagnesium carbonate. The regioselective nature of this reaction is consistent with the findings of Crombie, *et al.*, in an analogous case.[3]

Dimethyl β-Ketoadipate. A solution of 10.6 g (91.4 mmol) of levulinic acid (Eastman Technical) in 360 ml (920 mmol) of 2.56 *M* methylmagnesium carbonate in dimethylformamide (DMF)[2] was heated at 135° for 24 hr. The DMF was removed by distillation under vacuum at 60°. Trituration of the residue with ether gave after filtration and air drying of 136 g of yellow solid. The solid was suspended in 820 ml of methanol in a 3-l., three-necked, round-bottom flask equipped with a mechanical stirrer, a condenser, and a gas inlet tube. After cooling to −10°, hydrogen chloride was passed over the mixture until saturation had occurred. After standing overnight and warming to 25°, the mixture was concentrated at 40° under reduced pressure. The syrupy residue was poured on ice and the aqueous solution was extracted four times with chloroform. The organic extracts were washed with saturated bicarbonate solution and water and dried over anhydrous sodium sulfate. Distillation through an 1-in. Vigreux column gave 15.8 g (92% yield) of dimethyl β-ketoadipate as a colorless liquid: bp 94–96° (0.35 mm) [lit.[1] bp 110–111° (0.25 mm)]; nmr ($CDCl_3$) δ 2.70 (4 H, A_2B_2 multiplet), 3.49 (2 H, singlet), 3.62 (3 H, singlet), and 3.67 (3 H, singlet).

Registry No.—Dimethyl β-ketoadipate, 5457-44-3; levulinic acid, 123-76-2.

References and Notes

(1) E. C. Taylor and A. McKillop, *Tetrahedron*, **23**, 897 (1967).
(2) H. L. Finkbeiner and G. W. Wagner, *J. Org. Chem.*, **28**, 215 (1963).
(3) L. Crombie, P. Hemesley, and G. Pattenden, *Tetrahedron Lett.*, 3021 (1968).

Phenacyl Kojate Compared with Crown Ethers

Charles D. Hurd

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

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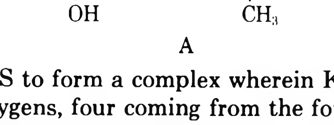
Crown ethers are of interest because of their ability to form complexes with sodium chloride and related salts. Following Pedersen's papers[1] there has been considerable development of this area. A comprehensive summary[2] has appeared recently. It lists 107 references, most of which are selected from the past decade. The area is diverse, and includes carbohydrates, for example. One obtains $C_{12}H_{22}O_{11} \cdot 2CH_3COOK$ when ether is added to a 0.02 *M* solution of sucrose[3] in ethanol that contains 0.4 *M* potassium acetate. Again, Sidgwick and Brewer[4] reported that the dihydrate of sodio-1-phenyl-1,3-butanedione was soluble in toluene whereas the anhydrous sodio derivative was insoluble. This observation was confirmed and extended by Bright, Milburn, and Truter.[4]

Nonactin is a neutral antibiotic, $C_{40}H_{64}O_{12}$, obtainable from *actinomyces*. It is a macrocyclic ester that yields four molecules of hydroxy acid A on saponification. Nonactin[5]

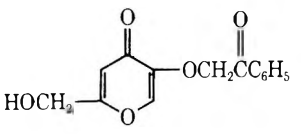

A

binds KCNS to form a complex wherein K^+ is surrounded by eight oxygens, four coming from the four ether oxygens and four from the four ester carbonyls. Also there are acidic

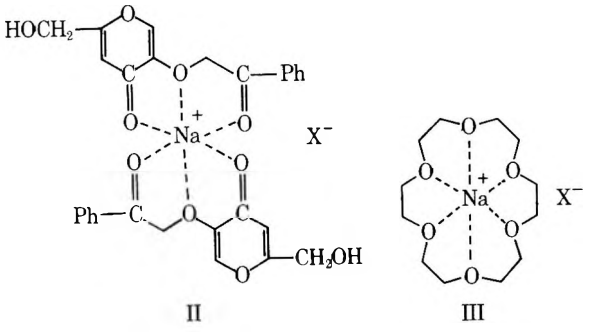
antibiotics[2] that complex with Na^+ or K^+, as monensin, nigericin, or dianemycin, which are open-chain rather than macrocyclic. Although the structures of these compounds show linear arrays of O-heterocyclic rings, the oxygens are so positioned as to surround the Na^+, thus resembling the macrocyclic esters and the crown ethers. There are but a few of the examples which have stimulated present interest.

In view of this activity, therefore, it may be helpful to those working in this field to call attention to a related but obscure observation of ours[6] which was reported in a different context 25 years ago. We observed a beautifully crystalline complex from methanol that involved 2 mol of phenacyl kojate and 1 mol of sodium halide, $2C_{14}H_{12}O_5 \cdot NaX$. The NaX was removable by treating the complex with water.

In phenacyl kojate (I) all oxygen atoms are separated by two carbon atoms, a feature which also holds for the conventional crown ethers. Structure II is proposed for the complex, by selecting OCCO sequences in phenacyl kojate that show cis relationships for the oxygens. This structure shows a striking similarity to III, the complex of a crown ether with NaX.



I



II III

There are two important differences, however, between II and III. In the first place, all oxygens in III classify as ether oxygens whereas in II four of the six participating oxygens are from carbonyl groups and the remaining two are more properly classified as ester oxygens than ether oxygens. This suggests that many other compounds that possess properly positioned nonether oxygens may also display complexing tendencies toward Na^+, K^+, or NH_4^+. Secondly, in III a single organic molecule holds all of the oxygens, whereas in II a pair of organic molecules are involved.

Registry No.—I, 49864-67-7.

References and Notes

(1) C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 2495, 7017 (1967); **92**, 391 (1970); H. K. Frensdorff, *ibid.*, **93**, 600, 4685 (1971); D. J. Sam and H. E. Simmons, *ibid.*, **94**, 4024 (1972); **96**, 2252 (1974); M. Svoboda, J. Hapala, and J. Zavada, *Tetrahedron Lett.*, 265 (1972); R. A. Bartsch and K. Wiegers, *ibid.*, 3819 (1972); D. J. Cram and J. M. Cram, *Science*, **183**, 803 (1974).

(2) M. R. Truter, "Structure and Bonding," Vol. 16, Springer-Verlag New York, New York, N. Y., 1973, pp 71–111.

(3) J. A. Rendleman, Jr., *J. Org. Chem.*, **31**, 1839 (1966).

(4) N. V. Sidgwick and F. Brewer, *J. Chem. Soc.*, **127**, 2379 (1925); D. Bright, G. Milburn, and M. Truter, *J. Chem. Soc. A*, 1582 (1971).

(5) B. Kilbourn, J. Dunitz, L. Pioda, and W. Simon, *J. Mol. Biol.*, **30**, 559 (1967); M. Dobler, J. Dunitz, and B. Kilbourn, *Helv. Chim. Acta*, **52**, 2573 (1973).

(6) C. D. Hurd and R. J. Sims, *J. Amer. Chem. Soc.*, **71**, 2443 (1949).

A Comparison between the Thermal and Photochemical 1,3-Cycloaddition Reactions of Ethyl 2-Methyl-3-phenylglycidate with Benzaldehyde. On the Thermal Fission of a Carbonyl Ylide

Jacques Kagan* and Bruce E. Firth

Chemistry Department, University of Illinois at Chicago Circle, Chicago, Illinois 60680

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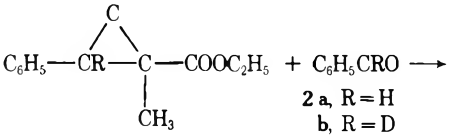
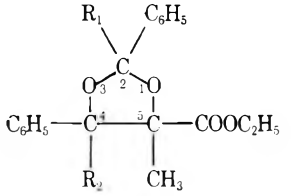
Compared to the wealth of information published on the photochemical behavior of oxiranes,[1] their thermochemistry has been particularly neglected. One puzzling question in this area concerns the requirements leading to the specific breaking of either the carbon–carbon or one of the carbon–oxygen bonds. In all the thermal 1,3-cycloaddition reactions of oxiranes published to date, there was cleavage of either the carbon–carbon bond[2] or one of the carbon–oxygen bonds,[3] but no competition between these two processes has been reported. This may have reflected either very different bond strengths in the oxirane or, in the case of comparable bond strengths, kinetic or thermodynamic factors in the product formation. In the cases of cycloaddition reactions with carbonyl dipolarophiles hitherto described, the products resulting from C–C or C–O bond breaking would have been chemically different and the effect of the latter factors could therefore have prevailed.

It was interesting to seek an example where *the same* structure would be obtained by either C–C or C–O bond breaking, and to use a label to determine the course of the cycloaddition reaction. We came across such a system, and recently described the photochemical cycloaddition reaction of ethyl 2-methyl-3-phenylglycidate (**1a**) with benzaldehyde (**2**) to give 2,5-diphenyl-4-methyl-4-carboethoxyl-1,3-dioxolane (**3**).[4] We proved by carbon-14 as well as by



1a, R = H
b, R = D

2a, R = H
b, R = D



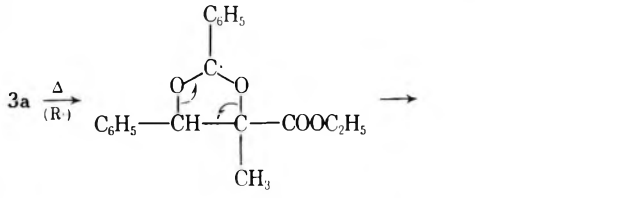
3a, $R_1 = R_2 = H$
b, $R_1 = D$; $R_2 = H$
c, $R_1 = H$; $R_2 = D$

deuterium[5] labeling experiments that **2a** had added to an oxirane in which the C–C and at least one C–O bond had cleaved competitively.

The cycloaddition of **1a** with **2a** to produce **3a** proceeded smoothly in a sealed tube at 235–280°. The treatment of **1a** with deuterated benzaldehyde (**2b**) in this temperature range yielded **3c** exclusively, the product of C–C bond cleavage in the oxirane. This was determined by nmr analysis, where the signal corresponding to H-4 was absent, and where the integration of the signal for H-2 represented a full proton. No alternate cycloaddition to **3b** followed by exchange of the acetal deuterium had taken place, since the thermal condensation of the deuterated glycidic ester **1b** and **2a** yielded **3b**, in which the signal for H-2 was absent, and where H-4 integrated for one full proton.

If we assume that, as in the photochemistry of 1,[4] the trapping of a carbon–oxygen-cleaved species by 2 would have been observed, we must conclude that within the sensitivity of the nmr technique the 1,3-cycloaddition reaction of 1 and 2 proceeds from exclusive carbon–carbon bond cleavage in the oxirane to the carbonyl ylide 4.

Extensive decomposition prevented the study of the cycloaddition reaction above 280°. When pyrolyzed alone, however, 3a was more stable and yielded two unidentified minor products at 300° for 30 min, in addition to unreacted starting material (50%), 2a (25%), and ethyl (*E*)-2-methylcinnamate (5, 25%), which was not detected in the thermolysis of 1a. A radical participation in the thermal decomposition of 1,3-dioxolanes has been recognized,[6] and such a mechanism would account for the formation of 5. Benzoic



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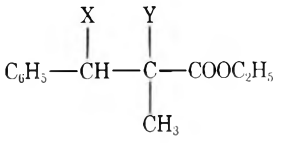
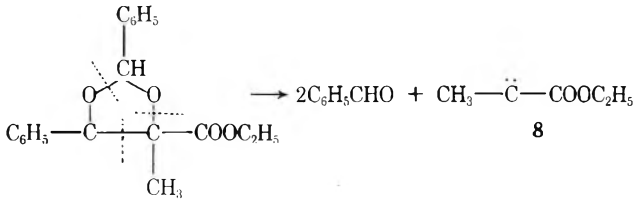
acid, stilbene, ethyl pyruvate, or 1a were not detected, and the isomerization of 3a into a benzoate such as 6 or 7, fol-



6, X = $OCOC_6H_5$; Y = H
7. X = H; Y = $OCOC_6H_5$

lowed by decomposition to 5, is held to be unlikely, since the pyrolysis of benzoates to olefins is known to yield benzoic acid quantitatively.[7]

The fragmentation of 3a, on the other hand, could have given two carbonyls and one carbene in three different manners. The formation of 5 by coupling of phenylcarbene and carboethoxylmethylcarbene[8] from the competition of at least two such processes is ruled out by the absence of the expected accompanying products. A cycloreversion reaction is required, however, for explaining the formation of 2a, and the most reasonable hypothesis is for the process giving 2 mol of 2a and 1 mol of 6, the latter yielding polymeric products following a hydrogen shift to ethyl acrylate.



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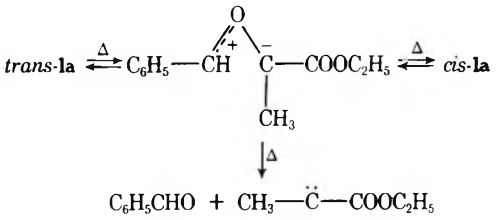
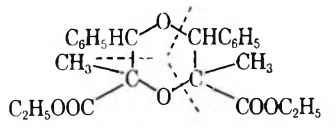
The photolysis of 1a had yielded 3a directly, resulting from the fission of two bonds to 2a (with the probable formation of 8, which we did not succeed in trapping), followed by cycloaddition of 1a and 2a. It is not known whether the cleavage of both bonds occurred simultaneously or not, and in this case whether or not the fission of the C–O bond preceded that of the C–C bond.

The thermolysis of 1a at 235° also led to the direct formation of 3a in low yield, in addition to cis–trans isomerization in the starting material. This result suggested that fission of the carbonyl ylide had occurred thermally, in contrast to Huisgen's experience with other carbonyl ylides at slightly lower temperatures.[2g] Probably each diastereoisomer of 1a yielded a different carbonyl ylide, and these interconverted thermally, but no information on the stereochemistry of the oxirane ring opening could be deduced from these experiments.



The synthesis of 1,4-dioxanes by condensation of oxiranes or glycols is well known.[8] Consequently, the benzaldehyde required for the direct conversion of 1a to 3a did not necessarily come from the direct fission of the carbonyl ylide, but could have been formed by fragmentation of a dioxane such as 9, 10, or 11, obtained by the dimerization of



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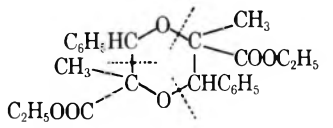

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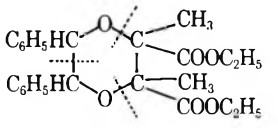

11

1a or 4. These fragmentation reactions would also have generated at least one of the following: 5 (*E* or *Z*), ethyl pyruvate, diethyl dimethylmaleate, or diethyl dimethylfumarate. Although not visible on the nmr spectrum of the mixture obtained in the thermolysis of 1, both diastereoisomers of 5 were detected by glc and gc–mass spectroscopy. None of the other products expected from the decomposition of 10 or 11 were observed.

Ethyl pyruvate was not stable under the conditions of the thermolysis, as shown by a control experiment in which a mixture with 1a was pyrolyzed for 2 hr at 275°. Consequently, it is not possible at this time to tell whether 5 originated with the decomposition of 3 or with that of 9, and whether or not the thermolysis of 1 produced 2 by fission of a carbonyl ylide remains to be determined.

Experimental Section

Ethyl 2-Methyl-3-deuterio-3-phenylglycidate (1b). A sodium ethoxide solution (from 1.1 g of Na in 50 ml of absolute EtOH) was added over 1.5 hr under N_2 to a solution of 5 g of 2b and 8.5 g of ethyl 2-bromopropionate in 10 ml of absolute EtOH with stirring in an ice bath. After stirring for 1 hr, 100 ml of H_2O was added and the solution was extracted with three 30-ml portions of ether which were combined, dried over $MgSO_4$, and evaporated. The yellow residue was distilled and yielded 4.1 g of 1b: bp 120–125° (3 Torr); nmr ($CDCl_3$) cis isomer at 0.9 (t, J = 7 Hz, 3 H), 1.77 (s, 3 H), 3.9 (q, J = 7 Hz, 2 H), and 7.28 ppm (s, 5 H), trans isomer at 1.3 (s, 3 H), 1.3 (t, J = 7 Hz, 3 H), 4.25 (q, J = 7 Hz, 2 H), and 7.28 ppm (s, 5 H).

Ethyl *trans*-2-Methyl-3-phenylglycidate (*trans*-1a). *trans*-α-Methylcinnamic acid (10.0 g) was treated with EtOH and H_2SO_4 at reflux and yielded 9.2 g of ester: nmr ($CDCl_3$) 1.25 (d, J = 7.5 Hz, 3 H), 2.05 (d, J = 1.5 Hz, 3 H), 4.15 (d, J = 7.5 Hz, 2 H), 7.23 (s, 5 H), and 7.6 ppm (q, J = 1.5 Hz, 1 H). This was epoxidized with *m*-chloroperoxybenzoic acid in $CHCl_3$ at reflux for 16 hr. After work-up, there was obtained 6.5 g of *trans*-1a: bp 121–123° (3 Torr); nmr ($CDCl_3$) 1.26 (s, 3 H), 1.29 (t, J = 7 Hz, 3 H), 4.20 (q, J = 7 Hz, 2 H), 4.29 (s, 1 H), and 7.27 ppm (s, 5 H).

Ethyl *cis*-2-Methyl-3-phenylglycidate (*cis*-1a). A mixture of glycidic esters from the Darzens reaction which contained 53% of the cis isomer was saponified with 0.5 equiv of KOH in absolute EtOH with stirring at room temperature for 3 min. After filtration of the pure trans salt, the solution was diluted with water and extracted with ether. The extract was dried, concentrated, and distilled at 97–99° (0.5 Torr) to yield 6 g of a mixture which was 94% *cis*- and 6% *trans*-1a. Pure *cis*-1a may be obtained by using 1.1 equiv of base with respect to the trans ester in the mixture.

Thermolysis of 1a. General Procedure. The Pyrex tubes were thoroughly washed with 6 *N* NaOH, water, and acetone and flame dried. After either the ester 1a or an equimolar mixture of 1 and 2 was introduced, the tube was sealed and placed in a sand bath. Identical results were obtained when soft glass washed as described above was used instead of Pyrex, or when the tubes were washed with concentrated HCl, water, and acetone and flame dried. Just before use, 2 was washed with aqueous $NaHCO_3$ and distilled from Zn dust. The sample of 2b was prepared according to Burgstahler, *et al.*,[9] and was pure from nmr.

A. A 250-mg sample of *trans*-1a was heated at 230° for 17 hr. Over 90% of the starting material was still present, but as a mixture of 84% trans and 16% cis isomers. Some 2a and 3a were also identified by glc and nmr.

B. A 250-mg sample of 1a containing 94% of the cis isomer was heated for 3.5 hr at 270°. Over 90% of 1a containing 60% of the trans isomer was recovered, in addition to small amounts of 2a, 3a, and 5.

C. A mixture of 1a (200 mg, *ca.* 50% trans) and 2a (100 mg) produced 16% conversion to 3a when heated at 235° for 2 hr, and 60% conversion to 3a when heated at 280° for 2 hr. However, decomposition took place, and no 3a could be isolated above 300°. The isomer of 3a obtained in these experiments was the same as that obtained photochemically, with nmr (CCl_4) at 0.90 (t, J = 7 Hz, 3 H), 1.75 (s, 3 H), 3.65 (q, J = 7 Hz, 2 H), 4.95 (s, 1 H), 6.00 (s, 1 H), and 7.25–7.90 ppm (10 H).[10] The sample of 3c obtained by thermolysis of 1a and 2b was identical, except for the absence of the 4.95-ppm signal, while the signal at 6.00 was missing in 3b from the thermolysis of 1b and 2a.

Thermal Stability of Ethyl Pyruvate. A mixture of 0.169 of ethyl pyruvate and 0.200 g of 1a (60% cis) was heated as above for 2 hr at 275°. Nmr and gc–mass spectra showed that no ethyl pyruvate was present in this reaction mixture.

Thermolysis of 3a. A crystalline sample of 3a did not show any change when heated in a sealed tube at 250° for 2 hr. After 0.5 hr at 300°, the nmr integration showed 50% 3a, 25% 2a, and 25% ethyl (*E*)-α-methylcinnamate. The assignments were confirmed by glc and glc–mass spectra against authentic samples. Neither 1a nor benzoic acid was detected.

Acknowledgment. We are indebted to the National Science Foundation for its opinion that "a study of the thermal reactions of oxiranes could have no practical applications since most laboratories are not equipped for performing reactions at the temperatures herein reported, and it will not provide answers to problems that people are interested in."

Registry No.—*cis*-1a, 7042-28-6; *trans*-1a, 7141-24-4; *cis*-1b, 52123-63-4; *trans*-1b, 52123-64-5; 2a, 100-52-7; 2b, 3592-47-0; 3a, 40707-69-5; ethyl 2-bromopropionate, 535-11-5; *trans*-α-methylcinnamic acid, 1895-97-2.

References and Notes

(1) G. W. Griffin, *Angew. Chem., Int. Ed. Engl.*, **10**, 537 (1971).
(2) (a) W. J. Linn and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 3657 (1965); (b) W. J. Linn, *ibid.*, **87**, 3665 (1965); (c) W. J. Linn and E. Ciganek, *J. Org. Chem.*, **34**, 2146 (1969); (d) A. Robert, J. J. Pommeret, and A. Foucaud, *Tetrahedron Lett.*, 231 (1971); (e) A. Robert, J. J. Pommeret, E. Marchand, and A. Foucaud, *Tetrahedron*, **29**, 463 (1973); (f) H. Hamberger and R. Huisgen, *Chem. Commun.*, 1190 (1971); (g) A. Dahmen, H. Hamberger, R. Huisgen, and V. Markowski, *ibid.*, 1192 (1971).
(3) H. H. Wasserman and E. H. Barber, *J. Amer. Chem. Soc.*, **91**, 3674 (1969); W. K. Anderson and T. Veysoglu, *J. Org. Chem.*, **38**, 2267 (1973).
(4) J. Kagan, J. T. Przybytek, B. E. Firth, and S. P. Singh, *Tetrahedron Lett.*, 5133 (1972).
(5) J. Kagan, B. E. Firth, and J. T. Przybytek, unpublished results.
(6) W. B. Guenther and W. D. Walters, *J. Amer. Chem. Soc.*, **73**, 2127 (1951).
(7) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).
(8) These reactions are usually acid catalyzed: C. B. Kremer and L. K. Rochen in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 1. However, thermal syntheses may also take place: E. J. Jahn and H. Hibbert, *Can. J. Res.*, **8**, 199 (1933).
(9) A. W. Burgstahler, D. E. Walker, Jr., J. P. Kuebrich, and R. L. Schowen, *J. Org. Chem.*, **37**, 1272 (1972).
(10) The chemical shifts reported for 3a in ref 4 were in error.

On the Perlactone *vs.* Dioxetanol Intermediates in the Thermal and Base-Catalyzed Autoxidation of Ethyl 2-Oxo-3-phenylbutyrate

David A. Mayers and Jacques Kagan*

Chemistry Department, University of Illinois at Chicago Circle, Chicago, Illinois, 60680

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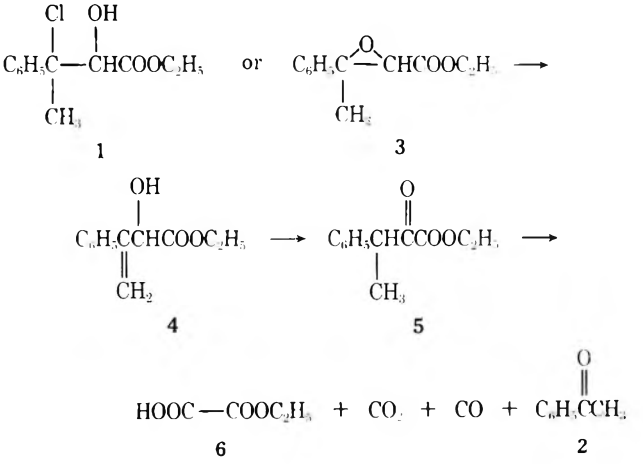
As part of a study on the mechanism of the migration of an ethoxycarbonyl group to an electron-deficient center,[1] the dehydrochlorination of ethyl 2-hydroxy-3-chloro-3-phenylbutyrate (1) at 132° was investigated. Surprisingly, acetophenone (2) was a major product.

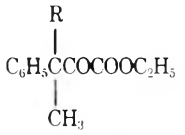
The shortest pathway from 1 to 2 involved the epoxide 3 obtained by dehydrochlorination, in which an oxygen atom was at the required position. While 3 was found to be converted into 2 under the acidic reaction conditions, nmr showed that both 1 and 3 initially yielded the allylic alcohol 4, which further isomerized into the keto ester 5 in the presence of an excess of acid. This product was the actual precursor to 2, and also yielded carbon monoxide, carbon dioxide, ethanol, and monoethyl oxalate at 132°. The conversion was accelerated by bubbling air through the solution, and was completely suppressed in the absence of oxygen. There was no oxidation with singlet oxygen, generated photochemically with rose Bengal as sensitizer, or obtained from the triphenyl phosphite–ozonide adduct.



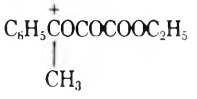
A mechanism patterned after the well-known cumene oxidation to phenol and acetone was considered, in which a hydroperoxide is decomposed with acid, and undergoes a phenyl migration from carbon to oxygen.[2] The corresponding rearrangement in 7 with either phenyl or methyl migration could not possibly give 2, and needs no further consideration.

The migration of the acyl moiety from carbon to oxygen[3] in the decomposition of 7 would produce a tertiary, oxygen-stabilized, benzylic cation intermediate 8.

Subsequent decomposition as shown in Scheme I, incorporating the molecule of water produced in the conversion of 7 to 8, would account for the observed products. For the sake of convenience, this decomposition is written as pro-



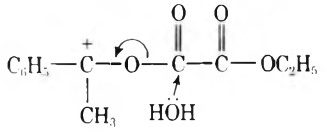
7, R = OOH
10, R = Br
11, R = OH



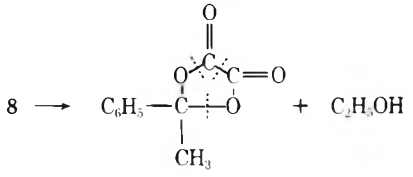
8

ceeding from the attack of water onto the carbonyl group which leads to **3** and **6**, the latter further decomposing to carbon monoxide, carbon dioxide, and ethanol. Alternatively, attack onto the other carbonyl with displacement of ethanol, and decarboxylation–decarbonylation, could also take place, but not as the exclusive pathway since it would not account for the presence of **6**. The process expressed in Scheme I may also be slightly modified to involve the cyclic intermediate **9** (Scheme II). In this case, competition with at least one other scheme producing **6** is also required. Finally, another hypothesis is that fragmentation occurred directly from **7** without prior group migration (Scheme III). Control experiments showed that the oxalate was only partially stable under the reaction conditions, and an exact determination of its contribution to the formation of carbon monoxide, carbon dioxide, and ethanol could not be obtained.

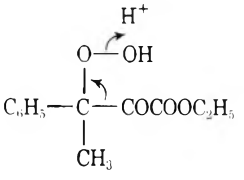
Scheme I



Scheme II



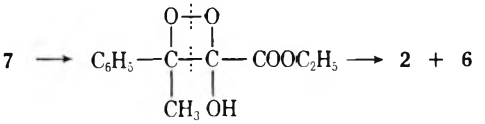
Scheme III



The synthesis of **7** was attempted, by alkaline 90% hydrogen peroxide treatment of the bromide **10**. We did not succeed in isolating the desired product down to −40°, and the formation of **2** was observed as soon as any reaction of **10** was detected. Although the nucleophile could either displace the bromide or attack one carbonyl, the former was suggested by the isolation of the substitution product **11** when water was substituted for hydrogen peroxide in this experiment. No reaction took place when this treatment of **10** was performed in acidic or neutral medium.

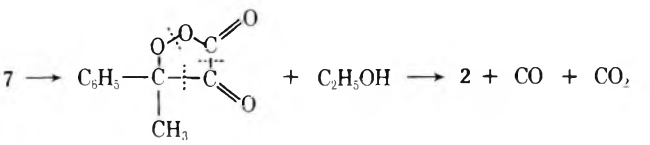
The mechanism for the conversion of **7** to **2** in basic solution need not be identical with that in acidic medium. Here the only reaction products were carbon monoxide, carbon dioxide, and ethanol. The often proposed mechanism for the degradation of α-hydroperoxy carbonyl compounds in neutral or alkaline medium does not apply,[4] since, as shown in Scheme IV, a dioxetanol intermediate would have produced monoethyl oxalate, which was proved to be stable under the reaction conditions.

Scheme IV



A mechanism which accounts for all the experimental facts in the base-catalyzed autoxidation of **5** involves cyclization of the presumed hydroperoxide intermediate **7** onto the ester carbonyl, giving an α-ketoperlactone **12** (Scheme V).

Scheme V

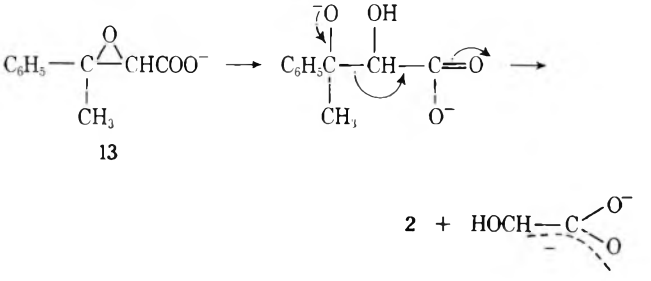


12

Although perlactones have been known since 1966,[5] and some have even been formed from β-hydroperoxy esters,[6] there is no record of any with an α-carbonyl, and this work suggests their thermal lability.

The mode of fragmentation proposed for **12** is analogous to one pathway observed in the thermolysis of simple perlactones[7] where a carbene must have been generated beside the ketone and carbon dioxide and which, understandably, required a much higher temperature than for the elimination of the stable carbon monoxide fragment. The extent to which the mechanisms expressed in Schemes IV and V contribute to the formation of **2** in the thermolysis of **1** or in the autoxidation of **5** in addition to those suggested in Schemes I–III is unknown.

Two reports of unexpected formation of acetophenone came to our attention. House and Blaker found that sodium β-phenyl-β-methylglycidate (**13**) yielded **2** beside the expected 2-phenylpropionaldehyde (**14**) when heated in aqueous solution.[8] The amount of **2** was considerably reduced (from 32 to less than 2%) when the salt was acidified at 0°. The difference was attributed to the intervention of a base-catalyzed retro-aldol reaction following opening of the epoxide. No explanation was provided for the formation of **2** in the acid-catalyzed reaction.



13

While the retro-aldol cleavage of β-hydroxy esters occurs either in base[9] or in acid,[1c] that of β-hydroxy acids is only known in acid medium.[10] The enolate ion of a carboxylic acid is only formed with great difficulty, and is therefore not expected to be a good leaving group. The autoxidation of **14** provides a more reasonable explanation for the presence of **2** in House and Blaker's experiments. The base-catalyzed treatment of **13** was repeated as described, with a control solution treated identically, but under nitrogen. The amount of **2** was found to be small in both cases (less than 3%), but the latter had about one-sixth the amount of **2** found in the former (nmr determination just following immediate work-up). As expected, the yield of **2** increased

markedly when the sample of **14** was allowed to stand in the presence of base without nitrogen protection.

The warning by House and Blaker[8] that any procedure involving heating a glycidic ester with aqueous alkali as part of the degradation to a carbonyl compound was undesirable is no longer justified. To the extent that saponification precedes glyceric ester formation (we know of no exception) the real problem rests with the protection of the initially formed carbonyl product from further autoxidation, easily solved by running the reaction under nitrogen.

Thummel and Rickborn reported the unexpected formation of **2** in the base-induced rearrangement of 1-methyl-2-phenyloxirane (**15**, 94% trans), and commented on the absence of analogy for the production of this material in the literature.[11]

A similar treatment of *trans*-1,2-diphenyloxirane had been reported to yield diphenylacetaldehyde,[12] and **14** was therefore expected from **15**. Its absence, and the failure by the authors to mention any protection from oxygen in the base-catalyzed treatment of **15**, point to the autoxidation of **14** as the most satisfactory explanation for the formation of **2** in these experiments.

Experimental Section

***threo*- and *erythro*-Ethyl 2-Hydroxy-3-chloro-3-phenylbutyrate (1).** Ether saturated with HCl (100 ml) was added to 10 g of **3**[13] frozen in liquid nitrogen. The mixture was stirred while being allowed to melt, and was then kept in a refrigerator for 23 hr. After concentration under vacuum, the residue crystallized from petroleum ether. It was recrystallized to yield 10.55 g of **1**, mp 53–59°.

Anal. Calcd for $C_{12}H_{15}O_3Cl$: C, 59.42; H, 6.22; Cl, 14.60. Found: C, 59.44; H, 6.22; Cl, 14.59.

Ethyl 2-Hydroxy-3-phenyl-3-butenoic Acid (4). A solution of 5 g of **3** in 25 ml of C_6H_5Cl was refluxed for 16.5 hr after HCl had been bubbled through for 5 min. The solvent was removed and nmr showed the crude product to be **4**, at least 90% pure. It was distilled bulb-to-bulb at 70° (0.07 Torr): nmr ($CDCl_3$) 0.95 (t, J = 7 Hz, 3 H), 4.07 (q, J = 6.75 Hz), and 4.08 (q, J = 7 Hz, total 2 H), 4.57 (s, 1 H, exchanges with D_2O), 5.28 (s, 1 H), 5.56 (s, 1 H), 5.60 (s, 1 H), 7.30 (m, 3 H), and 7.55 ppm (m, 2 H).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.85; H, 6.84. Found: C, 69.61; H, 7.11.

Ethyl 2-Oxo-3-phenylbutyrate (5). A solution of 10 g of **4** and 0.6 g of *p*-toluenesulfonic acid in 60 ml of C_6H_5Cl was refluxed for 30 hr. The solvent was removed under vacuum, and the residue was dissolved in ether, extracted with aqueous $NaHCO_3$, and dried over $MgSO_4$. The product, over 90% pure by nmr, was distilled and yielded **5**: bp 65° (0.07 Torr); nmr ($CDCl_3$) 1.13 (t, J = 7 Hz, 3 H), 1.80 (d, J = 7 Hz, 3 H), 4.07 (q, J = 7 Hz, 2 H), 4.38 (q, J = 7 Hz, 1 H), and 7.18 ppm (s, 5 H).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.92; H, 6.95.

Ethyl 2-Oxo-3-bromo-3-phenylbutyrate (10). To a refluxing solution of 7.50 g of **5** and 8.1 g of *N*-bromosuccinimide in 190 ml of CCl_4, 0.30 g of benzoyl peroxide was added over 3 hr. After another 18-hr reflux, the mixture was cooled, filtered, and concentrated under vacuum. The crude product was over 90% pure: bp 145° (3.5 Torr); nmr ($CDCl_3$) 1.15 (t, J = 7 Hz, 3 H), 2.22 (s, 3 H), 3.02 (q, J = 7 Hz, 2 H), and 7.33 ppm (m, 5 H).

Decomposition of 1. The bottom of a nmr tube containing about 0.20 g of **1** was immersed in refluxing C_6H_4Cl, contained in a flask fitted with a condenser which also cooled the top of the nmr tube. The progress of the reaction at 132° was monitored by nmr between 15 min and 54 hr. **2** was identified by comparison with an authentic sample (nmr, tlc, and glc), and **3**, **4**, and **5** were also detected by nmr.

Decomposition of 3. A sample of **1** containing a trace of HCl was heated as above. After 1.25 hr at 132°, **4** was formed in over 90% yield. In another experiment, the nmr tube containing 0.10 g of **3** and 0.01 g of **1** was sealed. After 63 hr at 132°, **5** had been formed in over 90% yield. In both cases **2** was detected by its characteristic signals at 2.5 and near 7.9 ppm in the nmr.

Decomposition of 5. The air used for the oxidation was purified through $PdCl_2$ in 0.005 *M* HCl, followed by solid NaOH and Linde molecular sieves. The sample of **5** was heated to 132 or 155° for 16 hr in the presence of a stream of air, which was then run into a trap cooled in liquid nitrogen. After reaction, this trap was allowed to warm up, and the gases released were passed through successive traps containing (a) NaOH and molecular sieves, (b) concentrated H_2SO_4, (c) saturated $Ba(OH)_2$, (d) aqueous $Pb(OAc)_2$, and (e) $PdCl_2$ in 0.005 *M* HCl.[14] The only product left in the reaction vessel was **2**, while CO_2 and CO were detected in traps c and e, respectively, and the nongaseous products left in the first trap were EtOH, monoethyl oxalate, and **2**.

Treatment of 5 with Singlet Oxygen. A. Ozone was bubbled through a solution of 1.5 g of triphenyl phosphite in 40 ml of CH_2Cl_2 at −78° until the blue color persisted. The excess of O_3 was removed by a stream of N_2, 1.0 g of **5** was added, and the solution was allowed to warm slowly to room temperature.[15] Nmr of the mixture after removal of the solvent showed that no reaction had taken place.

B. Air was bubbled through a solution of 0.479 g of **5** and 0.034 g of rose Bengal in 250 ml of CH_3CN during its irradiation at 350 nm for 2 hr in a Rayonet reactor. After removal of the solvent, nmr showed that only a trace amount of **2** had been formed.

Attempted Synthesis of Ethyl 2-Oxo-3-phenyl-3-hydroperoxybutyrate (7). A solution of 0.552 g of **10** and 0.32 ml of 90% H_2O_2 in 5 ml of acetone was stirred for 50 min after the addition of 0.145 g of K_2CO_3. The gas evolved was shown to contain CO with $PdCl_2$ in HCl. After standing for another 105 min, the mixture was filtered and the filtrate was concentrated to yield pure **2**. The solid obtained had no CH bonds as shown by nmr in D_2O. Control experiments indicated that **2**, **5**, and **6**[16] were all stable under the reaction conditions. The same results were obtained when the reaction was run at 5° in H_2O with NaOH, 24° in dioxane with K_2CO_3, and −40° in THF with K_2CO_3. A similar result was also observed at 5° in ether with K_2CO_3, but unreacted **10** was still present. At 24° in THF with HCl, no reaction took place. When the reaction in acetone with K_2CO_3 was run with H_2O rather than H_2O_2, it yielded ethyl 2-oxo-3-phenyl-3-hydroxybutyrate without decomposition.

2-Phenylpropionaldehyde (14) from 3. The published procedure was followed exactly,[8] with the exception that no stirring was used. A control reaction under N_2 was also performed. Nmr analysis showed that the amount of **2** was about 3% in the former and less than 0.5% in the latter. The crude reaction product was treated with 2,4-dinitrophenylhydrazine, and yielded the derivative from **14**, mp 135°.

Air Oxidation of 14. Air was bubbled for 1 hr through a solution of 1.25 g of **14** and 0.15 g of KO-*t*-Bu in 30 ml of *t*-BuOH. After concentration under vacuum, the nmr of the CCl_4-soluble fraction of the residue showed that over 50% of **14** had been oxidized to **2**.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Registry No.—**1**, 52217-11-5; **2**, 98-86-2; **3**, 77-83-8; **4**, 30913-58-7; **5**, 24441-66-5; **10**, 52217-12-6; **14**, 93-53-8.

References and Notes

(1) (a) S. P. Singh and J. Kagan, *J. Amer. Chem. Soc.*, **91**, 6198 (1969); (b) J. Kagan, D. A. Agdeppa, Jr., and S. P. Singh, *Helv. Chim. Acta*, **55**, 2252 (1972); (c) J. Kagan and D. A. Agdeppa, Jr., *ibid.*, **55**, 2255 (1972).
(2) R. T. Morrison and R. N. Boyd, "Organic Chemistry," 3rd ed, Allyn and Bacon, Boston, Mass., 1973, p 893.
(3) F. W. Lichtenthaler and G. Bambach, *J. Org. Chem.*, **37**, 1621 (1972).
(4) E. P. Kohler and R. B. Thompson, *J. Amer. Chem. Soc.*, **59**, 887 (1937); W. v. E. Doering and R. M. Haines, *ibid.*, **76**, 482 (1954).
(5) F. D. Greene, W. Adam, and G. A. Knudsen, Jr., *J. Org. Chem.*, **31**, 2087 (1966).
(6) R. C. P. Cubbon and C. Hewlett, *J. Chem. Soc. C*, 2983 (1968); D. H. Gibson, H. L. Wilson, and J. T. Joseph, *Tetrahedron Lett.*, 1289 (1973).
(7) W. Adam and G. Santiago Aponte, *J. Amer. Chem. Soc.*, **93**, 4300 (1971).
(8) H. O. House and J. W. Blaker, *J. Amer. Chem. Soc.*, **80**, 6389 (1958).
(9) C. S. Rondestvedt, Jr., and M. E. Rowley, *J. Amer. Chem. Soc.*, **78**, 3804 (1956).
(10) D. Ivanoff, N. Marecoff, and B. Amidjine, *Bull. Soc. Chim. Fr.*, 1214 (1963).
(11) R. P. Thummel and B. Rickborn, *J. Org. Chem.*, **37**, 3919 (1972).
(12) A. C. Cope, P. A. Trumbull, and E. R. Trumbull, *J. Amer. Chem. Soc.*, **80**, 2844 (1958).
(13) C. F. H. Allen and J. van Allan, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 727.
(14) R. Böttger, *J. Prakt. Chem.*, **76**, 233 (1859).
(15) R. W. Murray and M. L. Kaplan, *J. Amer. Chem. Soc.*, **91**, 5358 (1969).
(16) E. Fourneau and S. Sabetay, *Bull. Soc. Chim. Fr.*, **43**, 859 (1928).

Correlation Diagrams and the Mechanism and Stereochemistry of the Photochemical Diels–Alder Reaction

Nicolaos D. Epiotis* and R. L. Yates

Department of Chemistry, University of Washington, Seattle, Washington 98195

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The Woodward–Hoffmann rules[1] dictate that [4s + 2s] concerted photocycloadditions are symmetry-forbidden reactions. According to such a formulation, the photocycloaddition of a diene and an olefin is expected to proceed *via* the symmetry-allowed least-motion [2s + 2s] pathway or the non-least-motion symmetry-allowed [4s + 2a] or [4a + 2s] pathway. The Woodward–Hoffmann analysis was carried out on the basis of nonpolar models and we recently proposed that there is a dichotomy between the stereoselectivities of nonpolar and polar photocycloadditions owing to the different types of orbital interactions obtaining in these two general classes of photoreactions.[2] Correlation diagrams can be used fruitfully to analyze the stereoselectivity and mechanism of nonpolar and polar photocycloadditions. In this note, we confine our attention to the case of the photochemical [4 + 2] (Diels–Alder) cycloaddition.

In a photocycloaddition reaction, one can define the donor (D) and the acceptor (A) cycloaddend by reference to their ground-state properties. There are two general photocycloaddition mechanisms.[3] Mechanism 1 constitutes an example of an adiabatic transformation and mechanism 2 an example of a diabatic transformation.[4] Mechanism 2 is the one most often encountered in photochemical reactions, in general. Now, we can distinguish between nonpolar and polar [2 + 2] cycloadditions and between semipolar and polar [4 + 2] cycloadditions.[5] A typical semipolar [4 + 2] cycloaddition is that of butadiene and ethylene. The correlation diagram for the photochemical cycloaddition of butadiene and ethylene is shown in Figure 1. It is assumed that one photoexcited cycloaddend attacks the other one in its ground state. The correlation diagram shows that the lowest excited state of the complex does not correlate with either the lowest excited state of the product or directly with the ground state of the product. Hence, [4s + 2s] photocycloaddition is forbidden to occur *via* mechanisms 1 or 2.

$$\begin{matrix} D^* + A \\ \text{or} \\ D + A^* \end{matrix} \longrightarrow [\text{complex}]^* \longrightarrow P^* \longrightarrow P \qquad (1)$$

$$\begin{matrix} D^* + A \\ \text{or} \\ D + A^* \end{matrix} \longrightarrow [\text{complex}]^* \longrightarrow P \qquad (2)$$

A typical polar [4 + 2] cycloaddition involves a butadiene substituted by electron donor groups and an ethylene substituted by electron acceptor groups. Electron donating groups raise the energy of both the HOMO and the LUMO of butadiene, the former more than the latter, and electron accepting groups act principally by lowering the energy of the ethylene LUMO while leaving the energy of the ethylene HOMO relatively unchanged. As a result, in polar [4 + 2] cycloadditions, the HOMO of the diene has higher energy than the HOMO of the dienophile, a situation similar to the one which obtains in semipolar cycloadditions. On the other hand, *the LUMO of the diene has also higher energy than the LUMO of the dienophile, a situation which is opposite to the one which obtains in semipolar cycloadditions.* The correlation diagram for polar [4 + 2] photocycloaddition is shown in Figure 2 and a major difference between semipolar and polar [4 + 2] photocycloadditions is revealed. Specifically, *the lowest excited state of the reaction complex is a locally excited complex in the former case but an excited charge-transfer complex in the latter case.* Furthermore, the correlation diagram shows that the excited charge-transfer complex does not correlate with the lowest excited state of the product but *it does correlate with the ground state of the product.* This implies that [4s

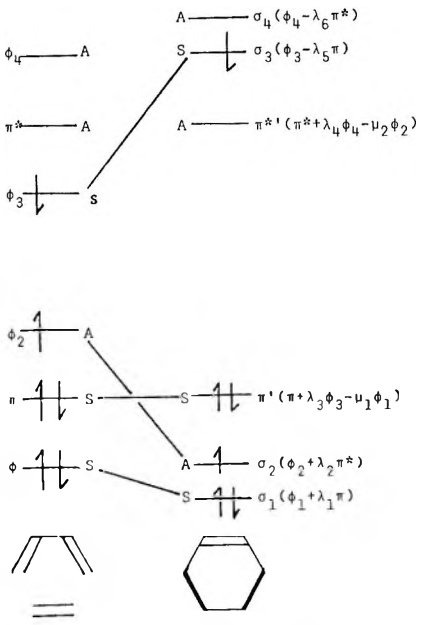

Figure 1. Correlation diagram for a semipolar [4s + 2s] photocycloaddition in which the reaction complex correlates only with a higher excited state $\sigma_1^2\sigma_2^1\pi'^2\sigma_3^1$, of the product as indicated on the diagram. The butadiene MO's are designated ϕ_1, ϕ_2, ϕ_3, and ϕ_4 and the ethylene MO's are π and π^*.

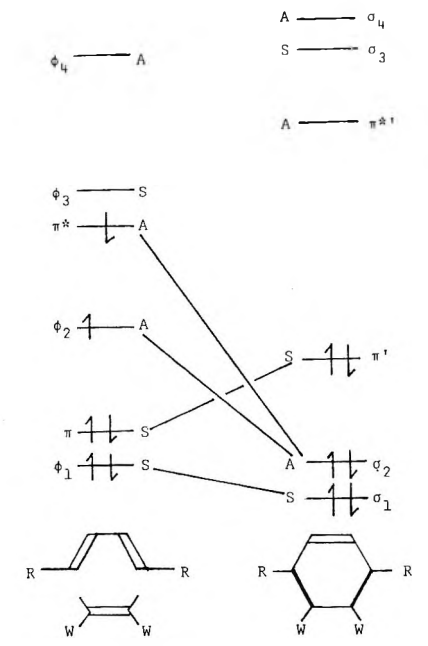

Figure 2. Correlation diagram for a polar [4s + 2s] photocycloaddition. The reaction complex correlates either with a higher excited state of the product, $\sigma_1^2\sigma_2^1\pi'^2\pi^{*\prime 1}$, or the ground state of the product, $\sigma_1^2\sigma_2^2\pi'^2$. The latter correlation is shown on the diagram. R = electron-releasing group, W = electron-withdrawing group. Only the butadienic and olefinic MO's are shown and the MO correlations are *intended* correlations.

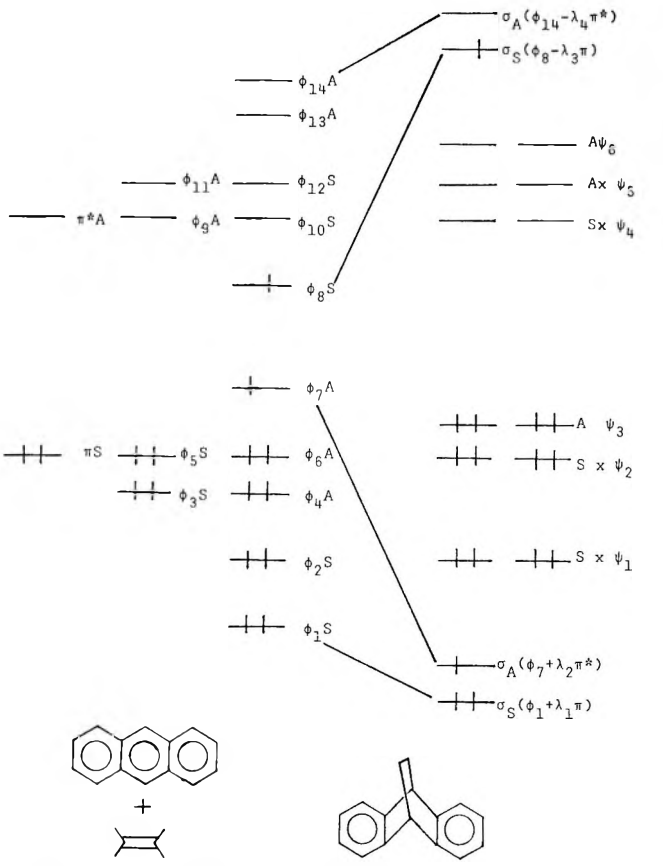

Figure 3. Correlation diagram for the [4s + 2s] photocycloaddition of anthracene and ethylene. The reaction complex correlates with a higher excited state of the product as shown in the diagram. The MO correlations are *intended* correlations.

+ 2s] cycloaddition is photochemically allowed to occur *via* mechanism 2. Similar conclusions are reached when butadiene is substituted by electron acceptor groups and ethyl-

$$\begin{matrix} D^* + A \\ \text{or} \\ D + A^* \end{matrix} \longrightarrow [D^+A^-]^* \longrightarrow P$$

ene by electron donor groups. Direct spectroscopic observations[6] indicate that the conversion of D* and A or D and A* to the excited charge-transfer complex is allowed and correlation diagrams reveal that the conversion of the latter complex to ground-state product is also allowed. In short, photochemical polar [4s + 2s] cycloadditions can indeed be very favorable.

Although the intricacies of correlation diagrams were fully discussed in the original work of Woodward and Hoffmann, it may be appropriate to stress some points. Thus the correlation diagram for the photoaddition of butadiene and ethylene involves crossing of levels of different symmetry and, thus, either a MO correlation diagram or a state correlation diagram provide a fully satisfactory depiction of the transformation. On the other hand, the correlation diagram for the photoaddition of a donor butadiene and an acceptor ethylene constitutes a simplified description of the transformation. Thus, if all the MO's of the two reactants were drawn, crossing of levels of the same symmetry would occur. However, this violation of the noncrossing rule could have been alleviated by the construction of state correlation diagrams which would have provided an adequate theoretical description of the transformation. Nonetheless, it is much simpler to construct MO correlation diagrams for systems where crossing of levels of the same symmetry occurs and discuss the so-called *intended* correlations of MO's. Hence, the correlation diagrams for the polar [4 + 2] photocycloadditions are perfectly adequate for our qualitative discussions.

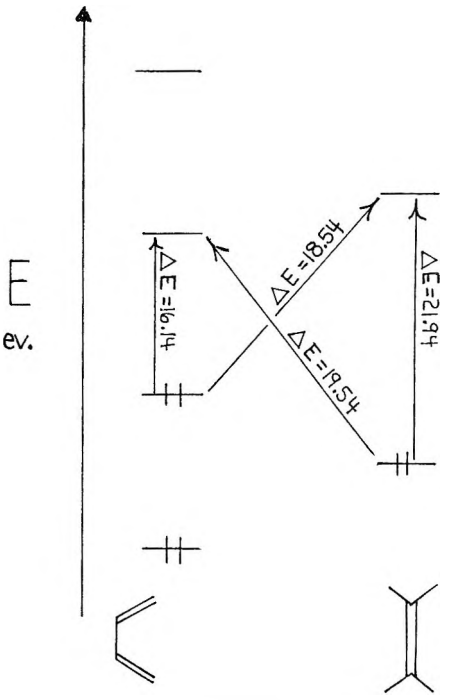

Figure 4. Interaction diagram for a semipolar [4 + 2] cycloaddition. The locally excited state is the lowest energy excited state. Energy levels from a CNDO/2 calculation.

The [4 + 2] photocycloadditions are not restricted to acyclic dienes and olefins. For example, aromatic molecules, like naphthalene, anthracene, etc., can potentially act as the diene component in photochemical [4 + 2] cycloadditions. The MO correlation diagram for the [4 + 2] photocycloaddition of anthracene and ethylene is shown in Figure 3. The intended MO correlations make it unambiguously clear that the situation is identical with that encountered in the case of the butadiene–ethylene photocycloaddition. A MO correlation diagram for the [4 + 2] photocycloaddition of donor anthracene–acceptor ethylene can be constructed and the conclusion drawn will be identical with those arrived at on the basis of the correlation diagrams for the photocycloaddition of donor butadiene–acceptor olefin.

We have sought to provide some kind of quantitative support for these ideas and we have calculated various diene–dienophile pairs in order to determine whether the locally excited or excited charge-transfer state will constitute the lowest excited state of the reactants to be correlated with the various states of the product. The calculation results shown in Figures 4–8 demonstrate clearly that in typical semipolar cycloadditions (Figures 4 and 7) the locally excited state is the lowest excited state, while in typical polar cycloadditions (Figures 5, 6, and 8) the excited charge-transfer state is the lowest excited state. The numbers in Figures 4, 5, and 6 were obtained by simple subtraction of CNDO/2 orbital energies and, thus, two electron correction terms are neglected in the calculation of the energy difference between a ground state and an excited state complex. A similar procedure is followed in Figures 7 and 8 where the orbital energies are eigenvalues of an effective one-electron Hamiltonian. We feel that the qualitative trends revealed by such an approach will not be altered significantly when electron interaction is incorporated in the

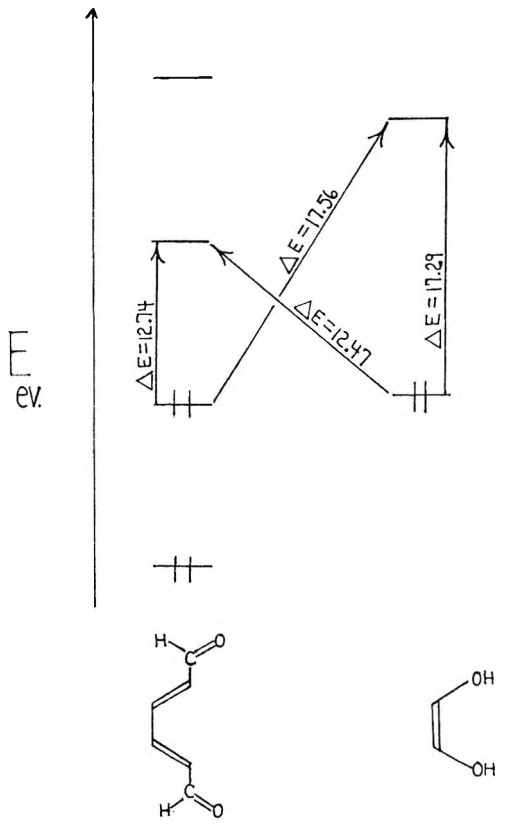

Figure 5. Interaction diagram for a typical polar [4 + 2] cycloaddition between an electron-deficient diene and an electron-rich olefin. The excited charge-transfer state is lower in energy than the locally excited state. Energy levels from a CNDO/2 calculation.

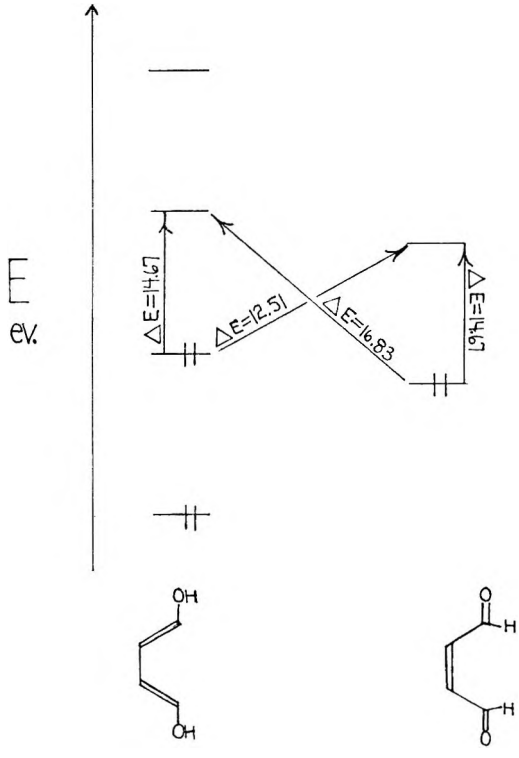

Figure 6. Interaction diagram for a polar cycloaddition between an electron-rich diene and an electron-deficient dienophile. The charge-transfer excited state is the lowest energy excited state. Energy levels from a CNDO/2 calculation.

theoretical treatment. Such an approach is discussed elsewhere.[7]

Our analysis is consistent with the following interesting

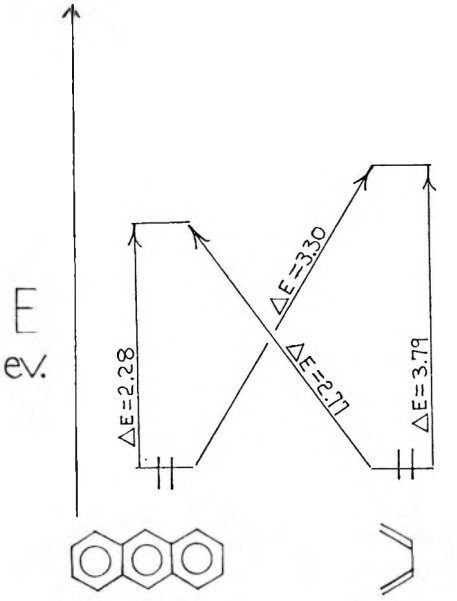

Figure 7. Interaction diagram for the cycloaddition of anthracene and butadiene. The locally excited state is lower in energy than the charge-transfer excited state. Energy levels from a Wolfsberg–Helmholtz–Mulliken calculation.

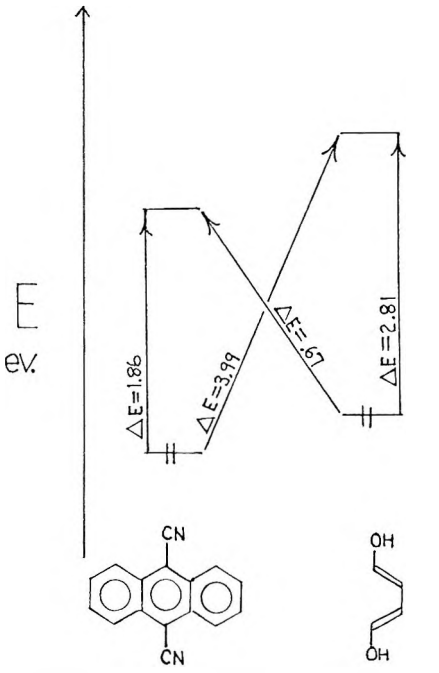

Figure 8. Interaction diagram for the cycloaddition of 9,10-dicyanoanthracene and 1,4-dihydroxybutadiene. The charge-transfer excited state is the lowest excited state. Energy levels from a Wolfsberg–Helmholtz–Mulliken calculation.

experimental facts.

(1) Anthracene adds to dienes stereospecifically in a [4s + 4s] manner, but 9-cyanoanthracene adds to dienes stereospecifically in a [4s + 2s] manner.[8]

(2) Retrograde homo-Diels–Alder reactions of azo compounds exhibit the same [4s + 2s] stereoselectivity under both thermal and photochemical conditions.[9]

(3) Maleic anhydride adds photochemically to benzene, a poor electron donor aromatic (ionization potential = 9.25 eV)[10] in a [2 + 2] manner.[11] On the other hand, it adds photochemically to anthracene, a good electron donor aromatic (ionization potential = 7.55 eV)[10] in a [4 + 2] manner.[12,13]

We suggest that polar [4 + 2] photocycloadditions can be useful synthetic reactions and that the orbital symmetry

approach[14] can be used in connection with many photochemical problems such as the effect of substituents on the mechanism and stereochemistry of photochemical pericyclic reactions.

Acknowledgment is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for the partial support of this research.

Registry No.—Butadiene, 106-99-0; ethylene, 74-85-1; anthracene, 120-12-7; 2,3-dimethyl-2-butene, 563-79-1; 2,4-hexadienediol, 3249-28-3; 1,2-ethenediol, 1571-60-4; 1,3-butadiene-1,4-diol, 42466-41-1; malealdehyde, 3675-13-6; 9,10-dicyanoanthracene, 1217-45-4.

References and Notes

(1) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.
(2) N. D. Epiotis, *J. Amer. Chem. Soc.* **94**, 1941, 1946 (1972). Similar ideas have been expressed by Herndon, *et al.*, in connection with the problems of carbonyl photocycloadditions: W. C. Herndon, *Tetrahedron Lett.* 125 (1971); W. C. Herndon and W. B. Giles, *Mol. Photochem.*, **2**, 277 (1970); *Chem. Commun.*, 497 (1969); W. C. Herndon, *Chem. Rev.*, **72**, 157 (1972).
(3) G. S. Hammond, *Advan. Photochem.*, **7**, 373 (1969).
(4) T. Forster, *Pure Appl. Chem.*, **34**, 225 (1973).
(5) N. D. Epiotis, *J. Amer. Chem. Soc.*, **94**, 1924 (1972).
(6) M. Ottolenghi, *Accounts Chem. Res.*, **6**, 153 (1973).
(7) N. D. Epiotis, in press.
(8) N. C. Yang and J. Libman, *J. Amer. Chem. Soc.*, **94**, 1405 (1972); N. C. Yang, J. Libman, L. Barrett, Jr., M. H. Hui, and R. L. Loeschen, *J. Amer. Chem. Soc.*, **94**, 1406 (1972).
(9) J. A. Berson and S. S. Olin, *J. Amer. Chem. Soc.*, **92**, 1086 (1970).
(10) R. S. Becker and E. Chen, *J. Chem. Phys.*, **45**, 2403 (1966).
(11) H. F. Angus and D. Bryce-Smith, *J. Chem. Soc.*, 4791 (1960).
(12) J. P. Simons, *Trans. Faraday Soc.*, **56**, 391 (1960).
(13) However, the [4 + 2] photoadditions of the esters of maleic and fumaric acids to anthracene appears to proceed *via* diradical intermediates rather than a stereoselective [4s + 2s] fashion: G. Kaupp, *Chimia*, **25**, 230 (1971). This may be due to the fact that these olefins are much inferior acceptors compared to maleic anhydride, for example.
(14) The correlation diagrams for semipolar and polar [4 + 2] photocycloadditions are constructed by reference to symmetrical reactants. However, the same conclusions are valid for unsymmetrical reactants, since the local symmetry of the ethylenic and butadienic MO's is the important factor.

The Activation Volume for Single-Bond Homolysis From Empirical Internal Solvent Pressure

J. Owens* and T. Koenig

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

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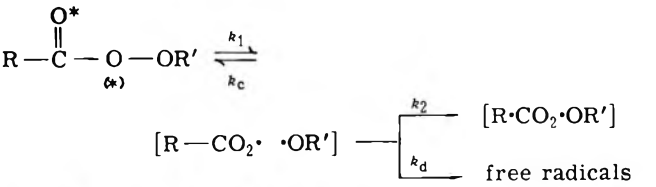
Neuman and coworkers[1] have measured apparent activation volumes for a number of free-radical initiators. These parameters (ΔV_e^*) were small for peresters previously proposed[2] to undergo concerted (C–C and O–O) decomposition and large for *tert*-butyl perbenzoate. The activation volumes were thus considered an additional criterion of mechanism. We,[3] as well as others,[4] have examined viscosity effects on overall rates of decomposition of peroxides. We have used Scheme I as a general one in analyzing the results quantitatively. Equations 1 and 2 (where k_o and k_s are observables) give the predictions of this scheme for overall disappearance of initiators.

Assuming k_d is the only viscosity-sensitive (interpretive) rate constant and *knowing* the value of k_1 allows the analysis of the k_o–fluidity dependence in terms of fraction recombination. Pryor and coworkers[4] have used essentially the same scheme and proposed extrapolation of $1/k_o$ *vs.* η^α to zero viscosity as a means of estimating the value of $1/k_1$. An alternative is to measure the rate constant for scrambling of carbonyl-^{18}O (k_s). Under the assumption above, the sum of $k_o + k_s$ (k_1) should be constant.

Scheme I



$$\frac{1}{(k_1/k_o) - 1} = \frac{k_2}{k_c} + \frac{k_d}{k_c} = \left(\frac{1}{f_{\text{recombination}}} - 1\right) = \frac{k_o}{k_s} \quad (1)$$

$$k_1 = k_o + k_s \quad (2)$$

These sums were not constant for either of the two cases which we investigated[3] (Table I, Scheme I; R = Ph, CH_3; R′ = *t*-Bu). We wish to point out that the positive activation volumes determined by the external pressure variation[1] imply that k_1 could only *fortuitously* be constant over the range of solvents investigated because of differences in internal solvent pressure.[5]

It is possible to circumvent the problems of calculating internal pressures by defining an empirical set of differential solvent pressures (DSP) from a reaction of known activation volume. This is analogous to the definition of Hammett[10] substituent constants from an arbitrary reaction. The apparent activation volume for *tert*-butyl perbenzoate is reported[11] to be +10.4 cc/mol in cumene and +12.9 cc/mol in chlorobenzene. Assuming that the activation volume in the hydrocarbon solvents which we have used is similar[12] and that the differential solvation energy is zero, the relative rates (Table I) can be used to determine the differential solvent pressures for the solvent series at 130° (Figure 1, Table I). A plot of ln ($k_o + k_s$) for the peracetate, also at 130°, *vs.* the DSP values is linear, giving an activation volume of +5 cc/mol (Figure 1), which is in agreement with

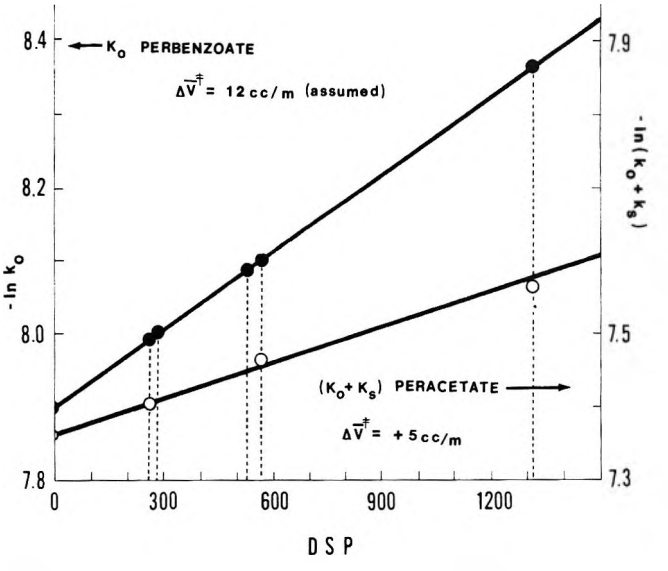


Figure 1. Activation volumes from empirical differential solvent pressures.

Table I
Rate Constants[a] for Decomposition and ^{18}O Scrambling at 130°

RCO_3-*t*-Bu

Solvent	k_o (R = CH_3)	k_s (R = CH_3)	$k_o + k_s$ (R = CH_3)	k_o (R = Ph)	k_s (R = Ph)	$k_o + k_s$ (R = Ph)	DSP,[b] atm
Hexane	50.8	13.1	63.9	3.72	0.16	3.88	0
Isooctane				3.36	0.20	3.56	288
Dodecane				3.08	(0.24)	3.42	534
60% hexane oil	44.3	16.6	60.9	3.39	(0.28)	3.67	263
30% hexane oil	38.0	19.3	57.1	3.04	(0.36)	3.40	571
Paraffin oil	31.3	20.8	52.1	2.33	(0.50)	2.83	1320

[a] $\times 10^5$ sec^{-1}; values in parentheses are interpolated from Figure 1, ref 3b. [b] Empirical differential solvent pressures from Figure 1 of this work.

Table II
Activation Volumes from DSP for RCO_3-*t*-Bu

R	Rate constant	ΔV^*_{DSP}, cc/mol[a]	ΔV^*_{ext}, cc/mol[b]	Registry no.
C_6H_5	k_o[3b]	(+12.00)	+10.4, +12.9[11]	614-45-9
C_6H_5	$k_o + k_s$[3b]	+8.0		
CH_3	$k_o + k_s$[3a]	+5.0	(+5)[1,c]	107-71-1
$CH_3OC_6H_4CH_2$	k_o[13]	+3.0	+3.1[16]	27396-21-0
$C_6H_5CH_2$	k_o[13]	−2.0	+1.7[11]	3377-89-7
$(CH_3)_2CH$	k_o[14]	−1.0	+1.6[15]	109-13-7

[a] Using the empirical differential solvent pressures derived here. [b] Using external pressure variation. [c] The value for a simple one-bond process.

expectations from the external pressure studies of Neuman.[1]

It is possible to estimate the k_s values for the perbenzoate by comparison with the corresponding hyponitrite (ref 3b, Figure 1). These values, summed with the appropriate k_o, give an activation volume of +8 cc/mol for the O–O bond homolysis of the perbenzoate. Table II contains the activation volumes for all the compounds for which we have data. The agreement with external pressure measurements is quite good if the sign inversions for the phenylacetyl[11,13] and isobutyryl[14] compounds are attributed to differential solvation. Solvation effects have similarly been invoked to explain the nonlinearity of the external pressure plots for these systems.[15]

Finally, we note that the apparent activation volume for the *tert*-butyl *p*-nitrophenylperacetate, as estimated from cohesive energy densities of the hydrocarbon solvents and the rate data of Pryor and Smith,[4a] is very large (+15 cc/mol). This reinforces their suggestion that this compound may be in part a one-bond initiator. A large value of ΔV^* is an indication of reversibility and not of intrinsic differences in transition state structures for the one-bond compared to two-bond process. The k_o/k_s method of estimating fraction return is not subject to the complications of variable k_1. Ruling out 1,3-sigmatropism,[14,16] they give the best estimate of reversibility in peroxide decomposition.

References and Notes

(1) R. C. Neuman, Jr., *Accounts Chem. Res.*, **5**, 381 (1972).
(2) P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).
(3) (a) T. Koenig, J. Huntington, and R. Cruthoff, *J. Amer. Chem. Soc.*, **92**, 5413 (1970); (b) T. Koenig, M. Deinzer, and J. A. Hoobler, *ibid.*, **93**, 938 (1971).
(4) (a) W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, **92**, 5403 (1970); (b) W. A. Pryor, E. Morkved, and H. Bickley, *J. Org. Chem.*, **37**, 1999 (1972).
(5) Neuman[6] has recently criticized studies of activation volumes through internal pressure on two grounds. The first was that the experimental data were compared with cohesive energy density rather than internal pressure. He showed that these two were not always correlated. Second, he showed negative correlations of some perester rates in solvents of rather different characteristics. He failed to point out the striking agreement of the difference in activation volumes for disproportionation and combination of ethyl radicals, observed by external pressure methods,[7] with that predicted previously from cohesive energy density correlations.[8,9] He also did not point out that a differential solvation energy of only 250 cal/mol completely swamps the effect of a differential internal pressure of 1000 atm for a reaction with an activation volume of 10 cc/mol. The latter comment applies to viscosity effects as well and our solvent series was chosen to minimize the differential solvation problem. Also, Figure 1 of ref 6 shows that internal pressure and cohesive energy density are related for hydrocarbons. In the original version of this work, correlations with calculated cohesive energy density were used. These gave essentially identical activation volumes, including the 12 cc/mol for the k_o values of the perbenzoate.
(6) R. C. Neuman, Jr., *J. Org. Chem.*, **37**, 495 (1972).
(7) C. M. Backman, S. Claesson, and M. Szwarc, *Trans. Faraday Soc.*, **66**, 3061 (1970).
(8) P. S. Dixon, A. P. Stefani, and M. Szwarc, *J. Amer. Chem. Soc.*, **85**, 2551 (1963).
(9) A. P. Stefani, *J. Amer. Chem. Soc.*, 90, 1694 (1968); *J. Phys. Chem.*, **73**, 1257 (1969).
(10) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940.
(11) R. C. Neuman, Jr., and J. V. Behar, *J. Amer. Chem. Soc.*, **91**, 6024 (1969).
(12) We assumed the value to be 12.000 cc/mol, the rounded average of the two reported values.
(13) T. Koenig and R. Wolf, *J. Amer. Chem. Soc.*, **91**, 2574 (1969).
(14) T. Koenig and J. G. Huntington, *J. Amer. Chem. Soc.*, **96**, 592 (1974).
(15) R. C. Neuman and R. P. Pankratz, *J. Amer. Chem. Soc.*, **95**, 8372 (1973).
(16) M. Goldstein and H. Judson, *J. Amer. Chem. Soc.*, **92**, 4220 (1970).
(17) R. C. Neuman, Jr., and J. V. Behar, *J. Org. Chem.*, **36**, 654 (1971).

Structural Effects on Intramolecular Carbene Reactions. Δ^3-Cyclopentenylmethylcarbene

Alfred Viola,* Shyamala Madhavan, and Robert J. Proberb

Department of Chemistry, Northeastern University, Boston, Massachusetts 02115

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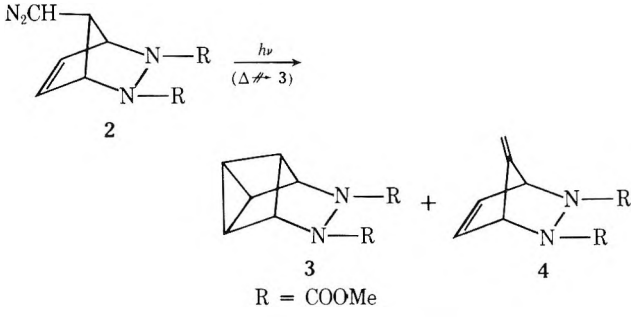
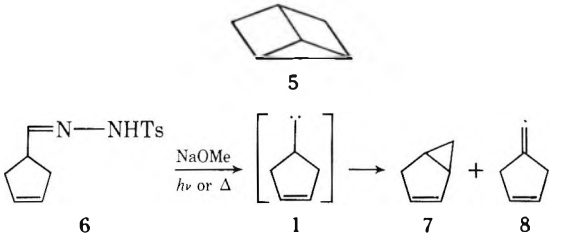
Intramolecular carbene insertions and cycloaddition reactions constitute a favorite route to small-ring polycyclic

structures. Yet there is little information available from the literature concerning circumstances favorable to such approaches. This report deals with the behavior of Δ^3-cyclopentenylmethylcarbene (1), which bears upon this problem.

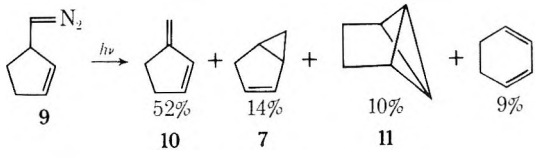
In the concerted cycloaddition of a singlet carbene to a double bond, to form a cyclopropane ring system, the p orbital of the carbene overlaps in a σ manner with one end of the π bond.[1] If the structure of the molecule is such that this requisite geometry cannot be attained, then a thermally generated singlet carbene cannot partake in such a reaction. A case in point is the report[3] of the reactions of **2**, the precursor to a carbene which incorporates the same structural features as **1** in a bicyclic framework. Failure of thermolysis of **2** to give any of the desired addition product, **3**, was ascribed to the inability of the strained framework to accede to the geometry required. Photolysis, however, provided **3** and **4** in about 2:1 ratio.



In the absence of the steric constraint inherent in the bicyclic framework of **2**, thermally generated singlet **1** might be expected to provide a route to tricyclo[2.2.0.0^{2,6}]hexane (**5**). Instead, the carbene, thermally generated from the tosylhydrazone **6**, afforded **7**[4] and **8**[5] in a 70:30 ratio, plus an unidentified, more volatile trace component.

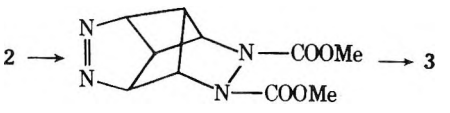


Photochemical decomposition of **6**, moreover, again afforded only **7** and **8** in a 70:30 ratio and again without any detectable amount[6] of **5**. These results differ substantially not only from those reported for **2**, but also from those reported[7] for **9**, the carbene from which is the Δ^2 analog of **1**.



We therefore conclude that neither singlet nor triplet carbene **1** can assume the requisite geometry for intramolecular cycloaddition and it follows that it is *not* the constraint inherent in the bicyclic framework which prevented thermal formation of **3** from **2**.

These results reinforce the suggestion of Trost and Cory[3] that the intermediate responsible for the formation of the cycloaddition product **3** is probably the 1,3-dipolar adduct **12** and an analogous process[8] may well account for the formation of **11**. The exaggerated puckering of the cyclopentene ring in the case of **2** places the diazo group closer to the double bond than is the case in the decomposition of **6**.



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One further comment seems apropos. Photolysis of **9** is reported[7] to favor the formation of the 1,2-insertion product, **10**, over the 1,3-insertion product, **7**, by a factor of 4, as is normally the case. In the case of **1**, however, the preference is reversed, as **7** predominates over **8** by a 2.5:1 ratio. This difference in behavior may owe its origin to a hydrogen radical abstraction pathway for the 1,3-insertion, which in **1** leads to a stabilized allylic radical.[9] The same factor would favor the production of **10** from **9**. A similar process in **2**, leading to 1,3-insertion, is obviously ruled out by geometry of **2**.

In conclusion, preexisting strain, as in **2**, is not necessarily a deterrent to a formal intramolecular cycloaddition *via* carbenoid species and may indeed aid in achieving the requisite geometry for formation of the internal 1,3-dipolar adduct, a likely intermediate from photolytic decomposition of appropriate diazo compounds.

Experimental Section

Preparation of Δ^3-Cyclopentenecarboxaldehyde Tosylhydrazone (6). Δ^3-Cyclopentenecarboxaldehyde was prepared as previously reported[10] and was isolated and purified by preparative vapor phase chromatography (F & M Model 776 equipped with an 8 ft × 0.75 in. column packed with 20% Triton X-305 on Chromosorb P). The tosylhydrazone, **6**, was obtained quantitatively by addition of tosylhydrazine to an equimolar amount of the aldehyde dissolved in cold benzene. Addition of excess pentane precipitated the desired derivative. The tosylhydrazone proved surprisingly unstable and became tacky, with perceptible darkening, upon attempted recrystallization or drying. Consequently a freshly precipitated sample was subjected to analysis (Spang Microanalytical Laboratories, Ann Arbor, Mich.), mp 83–86°.

Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.06; H, 6.10. Found: C, 58.86; H, 6.05.

Thermal and Photolytic Decomposition of Tosylhydrazone 6. Carbonium ion processes were avoided by use of "aprotic" conditions,[11] *i.e.*, freshly prepared $NaOCH_3$ and purified diglyme, and the participation of any such pathways is ruled out by the complete absence of any methoxy derivatives or any other products not ascribable to carbene insertions. A mixture of **6** with an excess of $NaOCH_3$ was heated, in diglyme, at 150–155° while the reaction vessel was vented with a stream of dry nitrogen which was then passed through a trap cooled with liquid nitrogen. The condensate consisted of methanol and a 35% yield of a 70:30 mixture (vpc, 10-ft column, 5% Apiezon on Chromosorp P) of bicyclo[3.1.0]hex-2-ene[4] (**7**), and 4-methylenecyclopentene[5] (**8**), which were identified by their characteristic nmr spectra. Photolysis was carried out on a similar mixture, with a 275-W sun lamp, while the mixture was maintained at room temperature. Prior to irradiation, the mixture was deoxygenated by sweeping it with a stream of dry nitrogen for a prolonged period. Irradiation was discontinued after evolution of nitrogen ceased and the remaining brown mixture was again flushed with nitrogen. The effluent, condensed in a trap cooled with liquid nitrogen, consisted of the same composition as that obtained from pyrolysis. That the observed reaction was indeed a photolysis, proceeding *via* the triplet carbene, is indicated by the fact that no visible reaction occurred when the deoxygenation step was omitted. The stability of products **7** and **8**, under these reaction conditions, was established by the fact that continued irradiation or heating, prior to flushing with nitrogen, failed to alter the product ratio or the amount produced.

Acknowledgment. We thank Professor J. M. Conia for the stimulating discussion which lead to this work.

Registry No.—**1**, 52123-97-4; **6**, 52123-98-5; **7**, 694-01-9; **8**, 14548-32-4; Δ^3-cyclopentenecarboxaldehyde, 20145-35-1; tosylhydrazine, 1576-35-8.

References and Notes

(1) Although this statement may be an oversimplification of the conclusions of ref 2, it reflects the commonly expressed interpretation thereof. (See, for example, ref 3.)
(2) R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968); N. Bodor, M. J. S. Dewar, and J. S. Wasson, *ibid.*, **94**, 9095 (1972).
(3) B. M. Trost and R. M. Cory, *J. Amer. Chem. Soc.*, **93**, 5572 (1971); B. M. Trost, R. M. Cory, P. H. Scudder, and H. B. Neubold, *ibid.*, **95**, 7813 (1973).
(4) P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, **30**, 771 (1965); M. P. Schneider and R. J. Crawford, *Can. J. Chem.*, **48**, 628 (1970).
(5) W. D. Huntsman, J. A. DeBoer, and M. H. Woosley, *J. Amer. Chem. Soc.*, **88**, 5486 (1966).
(6) No vpc peaks ascribable to this compound were detectable nor were there any nmr bands in the region described for this compound. The stability of **5** under these reaction conditions seems assured by the more rigorous conditions utilized in its previously reported preparations: D. M. Lemal and K. S. Shim, *J. Amer. Chem. Soc.*, **86**, 1550 (1964); R. J. Roth and T. J. Katz, *ibid.*, **94**, 4770 (1972).
(7) D. M. Lemal and K. S. Shim, *Tetrahedron Lett.*, 3231 (1964).
(8) The pyrazoline intermediate has recently been isolated in a similar system: E. Piers, R. W. Britton, R. J. Keziere, and R. D. Smillie, *Can. J. Chem.*, **49**, 2623 (1971).
(9) It is surprising that thermally and photochemically generated carbene **1** produce identical isolatable product mixtures. However, a thermodynamic equilibration process is unlikely in the absence of Lewis acids (*e.g.*, Ag^+), as described by Roth and Katz.[6] Furthermore, more highly strained **3** survives more rigorous conditions in its preparation[3] than those described herein.
(10) A. Viola and J. H. MacMillan, *J. Amer. Chem. Soc.*, **90**, 6141 (1968).
(11) A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **94**, 7081 (1972).

Structure and Reactivity of α,β-Unsaturated Ethers. XV.[1] The Acid-Catalyzed Hydrolysis of Alkyl Propenyl Ethers. The Relative Cis/Trans Reactivity

Tadashi Okuyama* and Takayuki Fueno

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan

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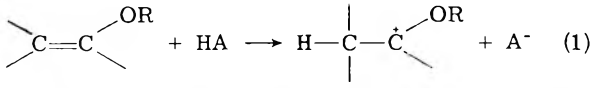
The acid-catalyzed hydrolysis of enol (α,β-unsaturated) ethers has widely been studied in recent years in the interest in its reaction mechanism.[2] It has been proved that the proton transfer to the unsaturated carbon is rate determining. This may be considered as a typical electrophilic addition reaction of the compounds of this class.



$$\text{C=C(OR)} + \text{HA} \longrightarrow \text{H—C—C}^{+}\text{(OR)} + \text{A}^- \qquad (1)$$

We already carried out kinetic studies on the hydrolysis and the cationic polymerization of a variety of α,β-unsaturated ethers from the viewpoint of the structure–reactivity relationship. It was found that the cis isomers of alkenyl alkyl ethers are generally more reactive than the corresponding trans isomers.[3-6] The greater reactivity of the former isomers was at first considered to be due to its lower stability in the ground state.[3,4] Similar discussion has been made to interpret the relative reactivity of cis and trans alkenes in terms of the strain relief on reaction.[7,8]

Later on, however, we have found that the cis isomers of β-chloro- and β-alkoxyvinyl ethers, which are more stable than the trans counterparts,[10] are also more reactive.[5,6] Explanation of these specific cases was made in terms of the polar nature of the reacting molecule; more polar cis isomers should more readily be attacked by an electrophile.[5,6] One example of this trend appearing in the earlier literature is the chlorination of a polar olefin, 1,2-dichloroethylene, in which the stable cis isomer[11] is more reactive.[12]

Nevertheless, we still feel it necessary to confirm the generality of the greater reactivity of cis olefins toward electrophiles. The most desirable for this purpose is to obtain reactivity data for a series of olefins structurally similar to each other but thermochemically different in terms of their geometrical stability. As such a class of olefins, we have chosen in the present study alkyl propenyl ethers; methyl and primary alkyl ethers are more stable in their trans form than in the cis form, while the reverse is the case for secondary and tertiary alkyl ethers.[10] The acid-catalyzed hydrolysis was studied as a typical reaction of these ethers. All the cis isomers were found to be more reactive than their trans counterparts, irrespective of the ground-state stability.

Results

The acid-catalyzed hydrolysis of unsaturated ethers was carried out in acidic 80% aqueous dioxane ([HCl] = 0.01–0.02 *M*). The reaction was followed by the gas chromatographic determination of ether concentrations.[3] Although ether was subjected to the kinetic measurements as an isomeric mixture, each geometric isomer showed excellent first-order decay separately, indicating the absence of concurrent geometrical isomerization of reactant isomers.[3] The reaction was first order in acid and an ether.

$$\text{rate} = k_2[\text{HCl}][\text{ether}] \qquad (2)$$

The rate measurements for methyl propenyl sulfide (8) was undertaken in the same way in 80% aqueous tetrahydrofuran. The kinetic features observed were much the same as those found for ethers.

Rate constants so obtained are summarized in Table I, together with some earlier results. The activation parameters, ΔH^* and ΔS^*, were calculated in the usual way (by plotting $\log k_2/T$ against $1/T$) and included in Table I. The final two columns of Table I give the thermodynamic data, ΔH° and ΔS°, for the cis–trans isomerization equilibria.[10] Negative values of ΔH^0 indicate greater thermochemical stability of the cis isomer in the liquid phase.

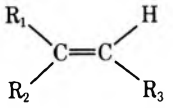
The data given in Table I show that the cis isomers are more reactive than the trans isomers for all the ethers studied here. The activation enthalpies, ΔH^*, of the former isomers are smaller than those for the latter, irrespective of their ΔH° values for the isomerization equilibria.

Discussion

Substituent Effects on the Reactivity. The reactivity of alkyl propenyl ethers increases in the order $CH_3 < C_2H_5 < i\text{-}C_3H_7 < t\text{-}C_4H_9$ for both the cis and trans isomers. The same order of the reactivity regarding the α-alkoxy group was previously observed with alkyl vinyl ethers[13,14] and alkyl ethynyl ethers.[15] This reactivity order of alkyl vinyl ethers is opposite to that expected from the electron density on the β-carbon atom of the vinyl group, which is deduced from the nmr data.[16-18] Undoubtedly, the reactivity should be accounted for from the stability of the transition state. The transition state of the reaction of the present concern resembles an intermediate carbonium ion,[3] which would be stabilized by the inductive electron donation by an alkyl group.

The reactivity of methyl propenyl sulfide (8) is about one-thousandth that of methyl propenyl ether (1), though the reaction medium is somewhat different. The same order of reactivity difference between S and O analogs was

Table I
Kinetic Data for the Acid-Catalyzed Hydrolysis[a] of α,β-Unsaturated Ethers



Compd	R_1	R_2	R_3	$10^4\ k_2$,[b] M^{-1} sec^{-1} 15°	25°	35°	45°	ΔH^*,[c] kcal/mol	ΔS^*,[d] eu	ΔH°,[e] kcal/mol	ΔS°,[e] eu
1c	H	CH_3	CH_3O	32.3	106	358		20.8	1.8		
										0.91	1.5
1t	CH_3	H	CH_3O	8.10	27.9	122		23.5	8.3		
2c[f]	H	CH_3	C_2H_5O	84.0	293	909		20.4	2.9		
										0.37	1.9
2t[f]	CH_3	H	C_2H_5O	22.6	90.3	299		22.2	6.5		
3c	H	CH_3	i-C_3H_7O	171	576	1720		19.9	2.4		
										−0.57	0.1
3t	CH_3	H	i-C_3H_7O	60.0	195	605		20.0	1.1		
4c	H	CH_3	t-C_4H_9O	303	870	2210		17.1	−5.8		
										−0.68	0.1
4t	CH_3	H	t-C_4H_9O	144	399	1080		17.3	−7.2		
5c[g]	H	C_2H_5O	C_2H_5O		3.23	11.1	36.0	20.7	−5.4		
										$[5c]_e/[5t]_e \sim 4$	
5t[g]	C_2H_5O	H	C_2H_5O		0.82	2.87	9.82	22.8	−0.9		
6c	H	Cl	C_2H_5O		0.68	2.37	7.03	21.6	−5.2		
										−0.66	0.8
6t	Cl	H	C_2H_5O		0.22	0.89	3.59	25.5	5.8		
7c	H	Br	C_2H_5O		2.38	7.72	21.5	20.1	−7.9		
7t	Br	H	C_2H_5O		0.72	2.85	8.78	23.0	−0.3		
8c[h,i]	H	CH_3	CH_3S			0.361	1.82	25.7	4.6		
8t[h,j]	CH_3	H	CH_3S			0.249	1.50	28.4	12.7		

[a] In 80% aqueous dioxane. [b] Given as an average of at least two measurements. [c] Accurate to within ±0.2 kcal/mol. [d] Accurate to within ±0.5 eu. [e] Values for the equilibrium trans ⇌ cis. Data were taken from ref 10. [f] Kinetic data were taken from ref 3. [g] Kinetic data were taken from ref 6. [h] Hydrolysis was carried out in 80% aqueous THF. [i] $k_2 = 4.92 \times 10^{-4}\ M^{-1}$ sec^{-1} at 55°. [j] $k_2 = 4.45 \times 10^{-4}\ M^{-1}$ sec^{-1} at 55°.

previously observed for the acetylenic ethers.[15,19] These differences will be ascribable to the diminished electron-donating conjugation ability of the thio group with 3p orbitals in the reactant and/or intermediate carbonium ion as compared with that of alkoxy group.

β-Alkoxy- and β-halogenovinyl ethers are less reactive than the propenyl ethers by a factor of 10^{-3} to 10^{-4}. In this case, the conjugative stability of the ground state due to the lone-pair electrons of a β substituent might be responsible for the reduced reactivity.

Relative Cis/Trans Reactivity. The results given in Table I show that all the cis isomers are more reactive than the corresponding trans isomers. The activation enthalpies, ΔH^*, are correspondingly greater for the trans isomers, irrespective of the relative cis/trans ground-state stability. That is, the greater reactivity of the cis isomers is enthalpy controlled in the ordinary temperature region. Similar tendency of the cis/trans reactivity was previously observed in the cationic polymerization of unsaturated ethers.[4-6,20-22]

It might safely be concluded that the greater reactivity of the cis isomers is quite general in electrophilic additions to olefins. Various kinetic results available in the literature[23] conform to this generalization. Some available examples which clearly do not fall in this generalization should be explained by certain other factors. For instance, hydrochlorination of *cis*-1-phenylpropene was concluded to be affected by the adverse steric effects arising from its nonplanar structure; if it were planar in structure, it would be (electronically) more reactive than the trans isomer.[24]

On the whole, the relative cis/trans reactivities in electrophilic addition reactions of olefins cannot be accounted for only by the ground-state properties of olefins. Some intrinsic electronic factor that operates on going from the ground to the transition state may control these reactivities. A theoretical molecular orbital calculation indeed demonstrates this point, which will be fully described elsewhere.[25] In brief, the Coulombic term of the interaction energy between an electrophile and an olefin at the transition state generally favors the cis structure of olefinic moiety. This Coulombic interaction must be a major factor contributing to the greater reactivity of the cis olefins in electrophilic additions.

On the contrary, in homolytic addition reactions where the Coulombic contribution is small, the charge-transfer interaction predominates and the trans isomers whose ionization potential is smaller are more reactive.[25] The charge-transfer interaction could well predominate even in electrophilic additions for exceptional cases, such as an olefin of low ionization potential plus an electrophile of low electron affinity. Such a case was actually encountered in sulfenyl chloride addition to 1-arylpropenes, in which the trans isomer was electronically more reactive.[26]

In conclusion, the cis olefins are generally more reactive in electrophilic addition reactions than the corresponding trans isomers, because of the favorable Coulombic interaction energy in the transition state.

Experimental Section

Materials. *cis*- and *trans*-Propenyl isopropyl ether (**3c** and **3t**)[21] and *cis*- and *trans*-β-chlorovinyl ethyl ether (**6c** and **6t**)[6]

were obtained as described previously, *cis*- and *trans*-propenyl methyl ether (**1c** and **1t**) were prepared in the same way as before;[3] cis/trans ~1.5, bp 45–46° (lit.[27] **1c**, 45.0° and **1t**, 48.5°). *cis*- and *trans*-propenyl *tert*-butyl ether (**4c** and **4t**) were prepared by the alcohol exchange from propenyl ethyl ether (a mixture of **2c** and **2t**).[28] The yield of a mixture of **4c** and **4t** (~4:1) was about 20%, bp 101–102° (lit.[29] **4c**, 101°).

cis- and *trans*-β-bromovinyl ethyl ether (**7c** and **7t**) were prepared from paraldehyde and bromine by the method of Jacobs, *et al.*[30] The isomeric composition (cis/trans) was ~3.5, bp 44–52° (20 mm) [lit.[30] 41–44° (19 mm)].

cis- and *trans*-propenyl methyl sulfide (**8c** and **8t**) were obtained by the rearrangement of allyl methyl sulfide,[31] bp 102–103° (lit.[32] 102°).

Geometrical structure of the ethers was assigned by pmr spectra.

Kinetic Measurements. The reaction of unsaturated ethers was carried out in 80% aqueous dioxane and the rates were measured gas chromatographically by the method described previously.[3] The hydrolysis of **8c** and **8t** was carried out in 80% aqueous tetrahydrofuran. In most cases a mixture of cis and trans isomers was subjected to hydrolysis but analyzed separately.

Acknowledgment. The authors thank Mr. Masao Nakada for his partial assistance in experimental work.

Registry No.—**1c**, 4188-68-5; **1t**, 4188-69-6; **2c**, 4696-25-7; **2t**, 4696-26-8; **3c**, 4188-64-1; **3t**, 4188-65-2; **4c**, 4188-71-0; **4t**, 4188-72-1; **5c**, 4884-01-9; **5t**, 1528-20-7; **6c**, 23679-21-2; **6t**, 23679-22-3; **7c**, 23521-49-5; **7t**, 16339-88-1; **8c**, 52195-40-1; **8t**, 42848-06-6.

References and Notes

(1) Part XIV: T. Okuyama, T. Sakagami, and T. Fueno, *Tetrahedron*, **29**, 1503 (1973).
(2) A. J. Kresge and H. J. Chen, *J. Amer. Chem. Soc.*, **94**, 2828 (1972), and references cited therein.
(3) T. Okuyama, T. Fueno, H. Nakatsuji, and J. Furukawa, *J. Amer. Chem. Soc.*, **89**, 5826 (1967).
(4) T. Fueno, T. Okuyama, and J. Furukawa, *J. Polym. Sci., Part A-1*, **7**, 3219 (1969).
(5) T. Okuyama, T. Fueno, and J. Furukawa, *J. Polym. Sci., Part A-1*, **7**, 2433 (1969).
(6) T. Okuyama and T. Fueno, *J. Polym. Sci., Part A-1*, **9**, 629 (1971).
(7) J. E. Dubois and G. Mouvier, *Tetrahedron Lett.*, 1622 (1965).
(8) See footnote 10 of ref 9.
(9) K. Yates and R. S. McDonald, *J. Amer. Chem. Soc.*, **93**, 6297 (1971).
(10) T. Okuyama, T. Fueno, and J. Furukawa, *Tetrahedron*, **25**, 5409 (1969).
(11) K. S. Pitzer and J. L. Hollenberg, *J. Amer. Chem. Soc.*, **76**, 1493 (1954).
(12) B. E. Swedlund and P. W. Robertson, *J. Chem. Soc.*, 630 (1947).
(13) D. M. Jones and N. F. Wood, *J. Chem. Soc.*, 5400 (1964).
(14) A. Ledwith and H. J. Woods, *J. Chem. Soc. B*, 753 (1966).
(15) E. J. Stamhuis and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **82**, 394 (1963).
(16) J. Feeney, A. Ledwith, and L. H. Sutcliffe, *J. Chem. Soc.*, 2021 (1962).
(17) H/ Yuki, K. Hatada, and M. Takeshita, *J. Polym. Sci., Part A-1*, **7**, 667 (1969).
(18) H. Yuki, K. Hatada, K. Nagata, and T. Emura, *Polym. J.*, **1**, 269 (1970).
(19) H. Hogeveen and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **82**, 375 (1963).
(20) T. Okuyama, T. Fueno, and J. Furukawa, *J. Polym. Sci., Part A-1*, **6**, 993 (1968).
(21) T. Okuyama, T. Fueno, J. Furukawa, and K. Uyeo, *J. Polym. Sci., Part A-1*, **6**, 1001 (1968).
(22) T. Higashimura, S. Kusudo, Y. Ohsumi, and S. Okamura, *J. Polym. Sci., Part A-1*, **6**, 2523 (1968).
(23) See, for the compilation of kinetic data, R. Bolton in "Comprehensive Chemical Kinetics," Vol. 9, "Addition and Elimination Reactions of Aliphatic Compounds," C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, Amsterdam, 1973, Chapter 1.
(24) K. Izawa, T. Okuyama, and T. Fueno, *Bull. Chem. Soc. Jap.*, **47**, 1477 (1974).
(25) K. Yamaguchi, T. Okuyama, and T. Fueno, to be published.
(26) K. Izawa, T. Okuyama, and T. Fueno, *Bull. Chem. Soc. Jap.*, **47**, 1480 (1974).
(27) M. Farina, M. Peraldo, and G. Bressan, *Chim. Ind. (Milan)*, **42**, 967 (1960).
(28) W. H. Watanabe and L. E. Conlon, *J. Amer. Chem. Soc.*, **79**, 2328 (1957).
(29) T. Higashimura, S. Kusudo, Y. Ohsumi, A. Mizote, and S. Okamura, *J. Polym. Sci., Part A-1*, **6**, 2511 (1968).
(30) T. L. Jacobs, R. Cramer, and J. E. Hanson, *J. Amer. Chem. Soc.*, **64**, 223 (1942).
(31) D. S. Tarbell and W. E. Lovett, *J. Amer. Chem. Soc.*, **78**, 2259 (1956).
(32) H. J. Boonsta, L. Brandsma, A. W. Wiegman, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **78**, 252 (1959).

Quasi-Favorskii Rearrangement. Synthesis of 1-Phenylcycloalkanecarboxylic Acids[1]

Calvin L. Stevens,* P. Madhavan Pillai,[2], and K. Grant Taylor

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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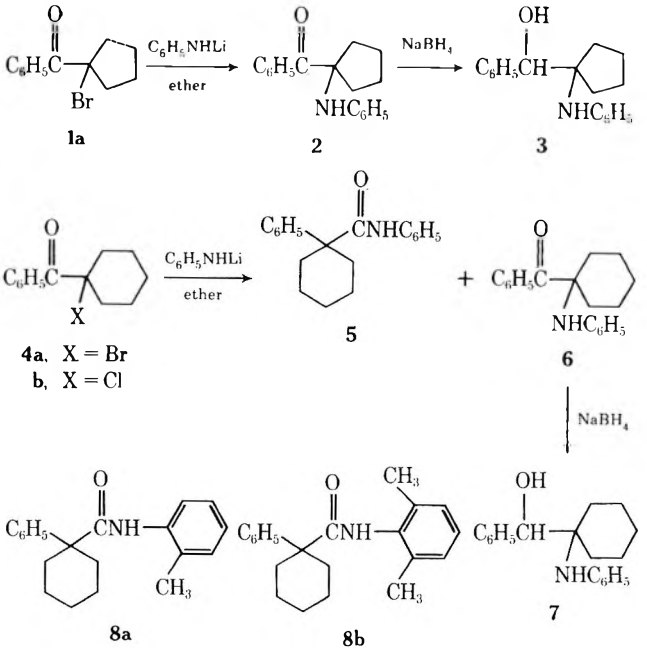
The skeletal rearrangement of α-halo ketones having an α′ hydrogen atom on treatment with certain nucleophiles such as hydroxides, alkoxides, or amines to give carboxylic acid salts, esters, or amides, respectively (Favorskii reaction) is well known and has been extensively investigated.[3,4] α-Halo ketones which do not have an α′ hydrogen atom[5,6] and certain α-halo ketones with α′ hydrogen attached to a bridgehead carbon atom[7,8] also undergo similar rearrangement, although by a different ("semibenzilic") mechanism, and may be called the "quasi-Favorskii reaction." Stevens and Farkas[5] and later Kirmann and Joschek[9] suggested that heterogeneous conditions are required for this rearrangement, as homogeneous conditions resulted in the direct replacement of the α halogen by the nucleophile. We now report a quasi-Favorskii rearrangement of α-halo ketones by the lithium salt of aromatic primary amines under homogeneous conditions. The resulting amides were hydrolyzed to the corresponding carboxylic acids, some of which are very difficultly obtained by other methods.

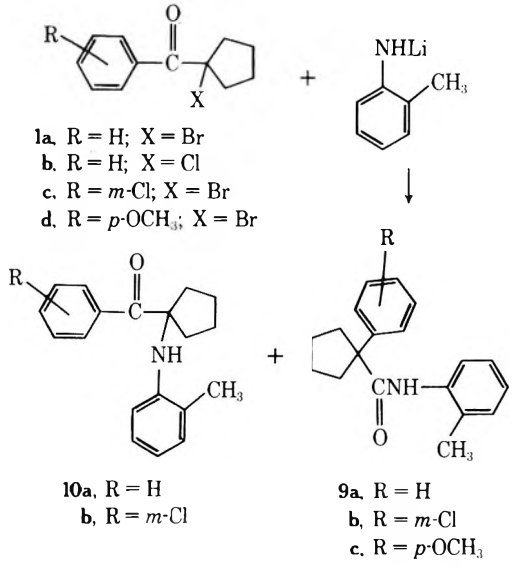
The reaction of α-bromo ketones with lithium anilide was investigated as a general method for the synthesis of α-anilino ketones. Although treatment of 1-benzoyl-1-bromocyclopentane[10] (**1a**) with lithium anilide in ether provided 87% of the amino ketone **2**, 1-benzoyl-1-bromocyclohexane[5a] (**4a**) under the same conditions gave only 30% of the corresponding amino ketone, **6**. The major product (55%) was 1-phenylcyclohexanecarboxanilide[11] (**5**), formed by a quasi-Favorskii rearrangement. When the α-chloro ketone,[5a] **4b**, was used in the place of **4a**, the proportion of the anilide[6] formed was increased to 62% at the expense of the anilino ketone, **6** (21%). This result is in agreement with an earlier observation[5a] in the rearrangement studies under heterogeneous conditions. Amino ketones **2** and **6** were further characterized by their reduction with sodium borohydride to the amino alcohols **3** and **7**, respectively.



It was observed earlier that in the case of α-chloroisobutyraldehyde, rearrangement was more effective using sodium *tert*-butoxide instead of sodium methoxide under heterogeneous conditions.[9] In order to find out whether this apparent steric influence was operative in homogeneous media as well, lithium anilide was replaced by lithium salts of *o*-toluidine and 2,6-dimethylaniline. The yields of the *o*-toluidide, **8a**, and 2,6-dimethylanilide, **8b**, were 70 and 72%, respectively (the amounts of amino ketones formed in these reactions were too small to be isolated). Also, bromo ketone **1a**, which did not rearrange at all with lithium anilide, gave 59% of the rearrangement product **9a** with lithium *o*-toluidide.

In order to study the effects of substituents on the phenyl group of the halo ketone, lithium *o*-toluidide was treated with halo ketones **1a–e** and the results are summarized in Table I. It may be noted that the increase in the yield of

Table I
Reaction of Lithium o-Toluidide with Substituted 1-Benzoyl-1-halocyclopentanes



1a, R = H; X = Br
b, R = H; X = Cl
c, R = *m*-Cl; X = Br
d, R = *p*-OCH_3; X = Br

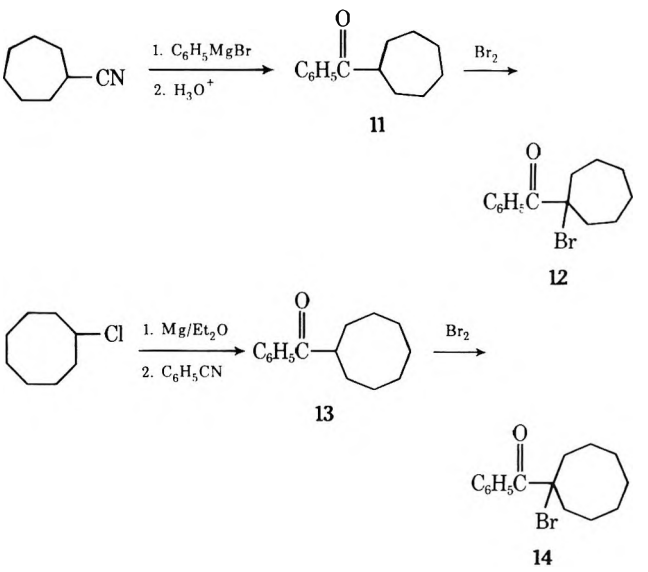
10a, R = H
b, R = *m*-Cl

9a, R = H
b, R = *m*-Cl
c, R = *p*-OCH_3

α-Halo ketone (ref)	Rearranged amide (yield, %)	Amino ketone (yield, %)
1a (10)	**9a** (59)	**10a** (20)
1b (12)	**9a** (68)	**10a** (10)
1c (13)	**9b** (13)	**10b** (50)
1d (13)	**9c** (80)	None

the rearranged product, *p*-methoxyphenyl > phenyl > *m*-chlorophenyl, is qualitatively in agreement with the relative migratory aptitudes of the three groups in pinacol-type rearrangements.[14]

Because of the significant difference in the yields of the rearranged amides from cyclohexyl and cyclopentyl ring systems, it was decided to study the influence of the ring size on the rearrangement. For this purpose, α-bromo ketones with seven- and eight-membered rings were synthesized as follows. Cycloheptyl phenyl ketone[15] (**11**) was prepared in 73% yield by treating phenylmagnesium bromide with cycloheptanecarbonitrile followed by acid hydrolysis. Bromination of **11** with bromine in carbon tetrachloride provided the required 1-benzoyl-1-bromocycloheptane (**12**). Similarly, conversion of cyclooctyl chloride[16] to the Grignard reagent followed by treatment with benzonitrile and hydrolysis gave cyclooctyl phenyl ketone (**13**) which was subsequently brominated to bromo ketone (**14**).



11

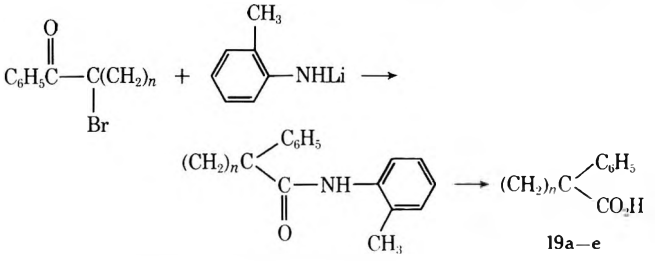
12

13

14

Rearrangements of bromo ketones with five- and six-membered rings have been discussed previously. Treatment of 1-benzoyl-1-bromocyclobutane[17] (**15**) with lithium *o*-toluidide gave only 19% of the rearranged amide, **16**. Several by-products formed in this reaction were not identified. Bromo ketones **12** and **14** yielded 62 and 48% of the o-toluidides, **17** and **18**, respectively. The formation of these rearranged amides in good yields from the α-bromo ketones could serve as an attractive synthetic pathway for the preparation of 1-phenylcycloalkanecarboxylic acids, some of which are very difficultly synthesized by alternate methods.[18,19] Because of the extremely hindered position of the amide carbonyl in the molecule, hydrolysis to the carboxylic acid was difficult. However, heating the toluidide with concentrated hydrochloric acid in a sealed tube at a temperature higher than its melting point offered a satisfactory method for the cleavage of the amide linkage in most cases. Results of these experiments are summarized in Table II.

Table II
Conversion of α-Bromo Ketones to Carboxylic Acids



19a–e

n	α-Bromo ketone	*o*-Toluidide (yield, %)	Carboxylic acid (yield, %)	Ref
3	15	16 (19)	**19a** (79)	18
4	1a	9a (59)	**19b** (73)	18
5	4a	8a (70)	**19c** (66)	5
6	12	17 (62)	**19d** (85)	19
7	14	18 (48)	**19e** (50)	

The availability of *exo*-2-bromo-*endo*-2-benzoylnorbornane[20] (**20**) made it possible to carry out the rearrangement with lithium anilide on a bromo ketone of known stereochemistry. Only one anilide, *endo*-2-phenylnorbornane-*exo*-2-carboxanilide (**21**), was obtained (67%), as might be expected from a concerted "semibenzilic rearrangement" mechanism.[21] Traces of amino ketone **22** were also formed.

Table III
Physical Properties of α-Amino Ketones and α-Amino Alcohols

Compd	Mp, °C	Molecular formula	Anal., % Calcd C	H	N	Found C	H	N
2	147	$C_{18}H_{19}NO$	81.48	7.22	5.28	81.55	7.12	5.48[a]
3 (HCl)	208 dec	$C_{18}H_{22}ClNO$	71.18	7.31	4.61	71.27	7.23	4.46
6	139–140	$C_{19}H_{21}NO$	81.68	7.58	5.05	81.64	7.64	5.04[b]
7 (HCl)	200 dec	$C_{19}H_{24}ClNO$	71.68	7.61	4.41	71.70	7.61	4.45
10a	120–121	$C_{19}H_{21}NO$	81.68	7.58	5.05	81.52	7.75	5.07
10b	99–100	$C_{19}H_{20}ClNO$	72.73	6.42	4.46	72.59	6.18	4.41[c]
22	200–201	$C_{20}H_{21}NO$	82.44	7.26	4.81	82.66	7.52	5.10[d]

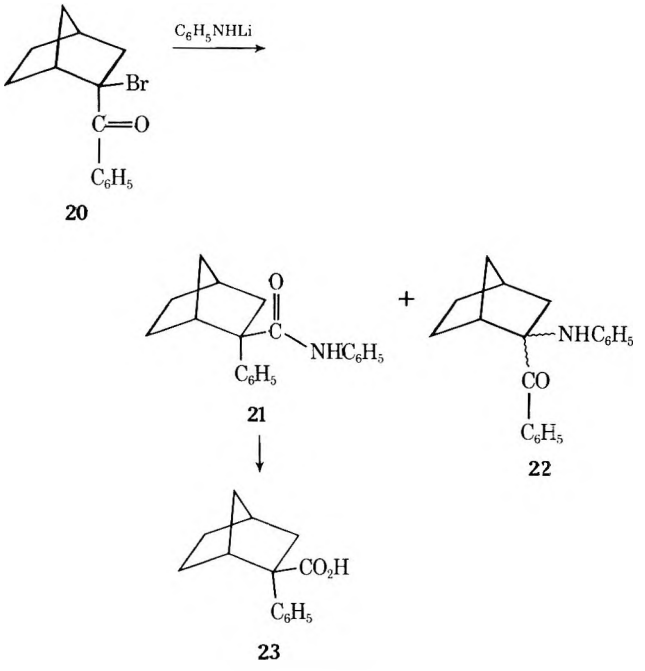
[a] Uv λ_{max} 285 nm (ε 2650), 248 (22,850); ir ($CHCl_3$) 3356 (NH), 1665 cm^{-1} (C=O). [b] Uv λ_{max} 287 nm (ε 2950), 248 (23,500); ir ($CHCl_3$) 3390 (NH), 1670 cm^{-1} (C=O). [c] Calcd: Cl, 11.30. Found: Cl, 11.27. [d] Uv λ_{max} 285 nm (ε 2820), 248.5 (23,300).

Table IV
Physical Properties of the Rearranged Amides

Compd	Mp, °C	Molecular formula	Anal., % Calcd C	H	N	Found C	H	N
8a	138	$C_{20}H_{23}NO$	81.87	7.90	4.77	82.08	7.86	4.87
8b	246–247	$C_{21}H_{25}NO$	82.04	8.20	4.56	82.28	8.24	4.57
9a	129–130	$C_{19}H_{21}NO$	81.68	7.58	5.05	81.79	7.55	5.12
9b	129–130	$C_{19}H_{20}ClNO$	72.73	6.42	4.46	72.55	6.39	4.56[a]
9c	111–112	$C_{20}H_{23}NO_2$	77.64	7.49	4.53	77.84	7.47	4.60
16	131–132	$C_{18}H_{19}NO$	81.48	7.22	5.28	81.43	7.17	5.41
17	82–83	$C_{21}H_{25}NO$	82.04	8.20	4.56	82.22	8.44	4.85
18	126–127	$C_{22}H_{27}NO$	82.20	8.47	4.36	82.39	8.67	4.56
21	144–145	$C_{20}H_{21}NO$	82.44	7.26	4.81	82.70	7.07	4.94

[a] Calcd: Cl, 11.30. Found: Cl, 11.22.

The structure of **21** was proved by its hydrolysis to the known *endo*-2-phenylnorbornane-*exo*-2-carboxylic acid[22] (**23**) and conversion of **23** back to **21** by standard procedures.



Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Thin layer chromatography was performed on 5 × 15 cm glass plates coated with silica gel H from Brinkmann Instruments using a hexane–ether (1:1) solvent system for developing unless otherwise mentioned. Compounds were detected by iodine vapor. Gas chromatographic analyses were performed on an F & M Model 810 instrument fitted with a flame ionization detector. A 3 ft × 0.25 in. 3% Carbowax 20M on Chromosorb W column was used. Nmr spectra were obtained in $CDCl_3$ using a Varian A-60 spectrometer with TMS as an internal standard. Infrared spectra were determined on a Perkin-Elmer Model 237B grating spectrophotometer. Ultraviolet spectra were obtained with a Cary Model 14 spectrophotometer in absolute ethanol. Elemental analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind.

General Procedure for the Reaction of α-Halo Ketones with the Lithium Salt of Aromatic Primary Amines. A solution of 20 mmol of the freshly distilled amine in 30 ml of anhydrous ether was stirred at room temperature under a nitrogen atmosphere and 20 mmol (12.5 ml of a 1.6 *M* solution) of butyllithium in hexane was added drop by drop. This homogeneous solution of the lithium salt of the amine was cooled to room temperature and a solution of 10 mmol of the bromo ketone in 20 ml of anhydrous ether was added dropwise with stirring. In most cases the reaction mixture remained homogeneous and the reaction was complete in 30 min as shown by tlc. The mixture was poured into cold water and extracted with ether. The ether layer was washed with 0.5 *N* HCl to remove the unreacted amine. If the ether solution showed only one product (either amino ketone or amide) by tlc, it was washed with water, dried (Na_2SO_4), and evaporated to dryness to give that single compound. If tlc indicated two products, the ether solution was washed repeatedly with 6 *N* HCl until all the amino ketone was separated from the amide. The ether layer was then washed with water, dried (Na_2SO_4), and evaporated to dryness to obtain the rearranged amide. The 6 *N* HCl solution was diluted with water and neutralized with $NaHCO_3$, the liberated amino ketone was extracted with ether and dried (Na_2SO_4), and the solvent was removed. The products were usually recrystallized from hexane for analysis. The melting points and analytical data of the amino ketones are given in Table III and those of the amides in Table IV.

Reduction of Amino Ketones to Amino Alcohols. A solution of 100 mg of 2 in 10 ml of CH_3OH was stirred with 200 mg of $NaBH_4$ for 12 hr at room temperature. The solvent was removed under reduced pressure, water was added, and the mixture was ex-

tracted with ether. The ether solution was dried (K_2CO_3) and evaporated to dryness and the gummy residue as redissolved in ether and treated with HCl in isopropyl alcohol. The product was recrystallized from ethanol–ether to give 90 mg (78%) of **3** as its HCl salt. Similarly 100 mg of **6** was converted to 110 mg (95%) of **7**, also characterized as its HCl salt. The physical properties of **3** and **7** are included in Table III.

General Procedure for the Hydrolysis of the Rearranged Amide. A mixture of 500 mg of the amide and 20 ml of concentrated HCl was heated in a sealed tube at 130–150° (about 10° above the melting point of the amide) for 24 hr. The reaction mixture was diluted with water and extracted several times with ether. The ether layer was extracted with a saturated solution of $NaHCO_3$. The bicarbonate solution was acidified with HCl, reextracted with ether, dried (Na_2SO_4), and evaporated to dryness. The residue was usually recrystallized from hexane to give the carboxylic acid in good yield. (See Table II.)

Cycloheptyl Phenyl Ketone (11). Freshly distilled bromobenzene (157 g, 1.0 mol) was converted to phenylmagnesium bromide using 24.0 g of magnesium. A solution of 61.5 g (0.5 mol) of cycloheptanecarbonitrile in 250 ml of dry ether was added drop by drop to the Grignard reagent while the mixture was mechanically stirred. After the addition was complete, the mixture was heated under reflux for 36 hr. It was cooled and 125 ml of 4 *N* HCl was carefully added followed by 250 ml of 4 *N* H_2SO_4. The ether was expelled by warming the mixture on a steam bath and the residue was heated under reflux with stirring for 24 hr. The cooled mixture was extracted with ether, washed with water followed by $NaHCO_3$ solution, and dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was fractionated at 0.1 mm. The fraction boiling at 100–110° (86 g) showed 3% impurities by gc. It was refractionated to give 75.2 g (75%) of **11**: bp 97–100° (0.05 mm); $n^{24}D$ 1.5410; 2,4-dinitrophenylhydrazone, mp 168–170° [lit.[15] bp 115–117° (0.2 mm); $n^{25}D$ 1.5405; 2,4-dinitrophenylhydrazone, mp 170–171°].

1-Benzoyl-1-bromocycloheptane (12). A solution of 3.2 g (20 mmol) of bromine in 25 ml of CCl_4 was added dropwise to a magnetically stirred solution of 4.04 g (20 mmol) of **11** in 25 ml of CCl_4. After the addition of bromine, stirring was continued for 2 hr. The solvent was removed *in vacuo* and the residue was evaporatively distilled (bath temperature 75°, 0.0005 mm) to give 5.06 g (90%) of **12**, $n^{24}D$ 1.5718, λ_{max} 251.5 nm (ϵ 7660).

Anal. Calcd for $C_{14}H_{17}BrO$: C, 60.02; H, 6.12; Br, 28.53. Found: C, 60.04; H, 6.06; Br, 28.47.

Cyclooctyl Phenyl Ketone (13). Cyclooctyl chloride[16] (103.5 g, 0.7 mol) was converted to cyclooctylmagnesium chloride in ether using 17.0 g of magnesium. A solution of 51.5 g (0.5 mol) of benzonitrile in 200 ml of ether was added dropwise and the mixture was stirred at room temperature for 3 hr and then heated under reflux for 12 hr. The mixture was cooled and 100 ml of 6 *N* H_2SO_4 was added carefully. The ether was boiled off and the residue was heated on a steam bath with stirring for 8 hr. The cooled mixture was extracted with ether, the ether layer was washed with water followed by $NaHCO_3$ solution and dried (Na_2SO_4), and the solvent was removed. The residue was fractionated at 0.02 mm. The fraction boiling at 112–115° (46.2 g) showed 2% impurities by gc. It was refractionated to give 30.3 g (28%) of **13**, bp 102° (0.01 mm). A sample was evaporatively distilled for analysis, $n^{25}D$ 1.5438.

Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.51; H, 9.38.

A portion of **13** was converted to its semicarbazone, mp 136–137°.

Anal. Calcd for $C_{16}H_{23}N_3O$: C, 70.30; H, 8.48; N, 15.37. Found: C, 70.03; H, 8.76; N, 15.48.

1-Benzoyl-1-bromocyclooctane (14). Ketone **13** (4.32 g, 20 mmol) was brominated as described for the preparation of **12**. The product was evaporatively distilled (bath temperature 110°, 0.01 mm) to give 4.7 g (80%) of **14**, $n^{25}D$ 1.5699.

Anal. Calcd for $C_{15}H_{19}BrO$: C, 61.05; H, 6.49; Br, 27.07. Found: C, 60.76; H, 6.62; Br, 26.66.

1-Phenylcyclooctanecarboxylic Acid (19e). A mixture of 500 mg of **18** and 10 ml of concentrated HCl was heated in a sealed tube at 110° for 12 hr and then at 135–140° for 12 hr. The mixture was diluted with water and extracted with ether. The ether layer was extracted with $NaHCO_3$ solution. From the neutral ether solution was isolated 210 mg (42%) of the starting amide, **18**. The bicarbonate solution was acidified with concentrated HCl, reextracted with ether, and dried (Na_2SO_4) and the solvent was removed. The residue was recrystallized from hexane to give 105 mg (50% based on the hydrolyzed amide) of **19e**, mp 103°.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.39; H, 8.63.

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Registry No.—**1a**, 6740-66-5; **1b**, 52217-42-2; **1c**, 52123-79-2; **1d**, 6728-52-5; **2**, 52123-80-5; **3** HCl, 52123-81-6; **4a**, 7500-66-5; **4b**, 1135-71-3; **6**, 52123-82-7; **7** HCl, 52217-43-3; **8a**, 52123-83-8; **8b**, 52123-84-9; **9a**, 52123-85-0; **9b**, 52123-86-1; **9c**, 52123-87-2; **10a**, 52123-88-3; **10b**, 52123-89-4; **11**, 6004-52-0; **12**, 52217-44-4; **13**, 6004-59-7; **13** semicarbazone, 52123-90-7; **14**, 52123-91-8; **15**, 51175-78-1; **16**, 52123-92-9; **17**, 52123-93-0; **18**, 52123-94-1; **19e**, 52123-95-2; **20**, 34546-66-2; **21**, 52123-99-6; **22**, 52123-96-3; lithium *o*-toluidide, 52217-45-5; bromobenzene, 108-86-1; cycloheptanecarbonitrile, 32730-85-1; cyclooctyl chloride, 1556-08-7; benzonitrile, 100-47-0; lithium anilide, 20732-26-7.

References and Notes

(1) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstract No. S-92.
(2) Abstracted in part from the Ph.D. Dissertation of P. M. Pillai, Wayne State University, 1968.
(3) For a review, see A. S. Kende, *Org. React.*, **11**, 261 (1960).
(4) F. G. Bordwell and J. G. Strong, *J. Org. Chem.*, **38**, 579 (1973), and references cited therein.
(5) (a) C. L. Stevens and E. Farkas, *J. Amer. Chem. Soc.*, **74**, 5352 (1952); (b) B. Tchoubar, *C. R. Acad. Sci.*, **228**, 580 (1950).
(6) J. M. Conia and J. Salaun, *Bull. Soc. Chim. Fr.*, 1957 (1964).
(7) (a) A. C. Cope and E. S. Graham, *J. Amer. Chem. Soc.*, **73**, 4702 (1951); (b) E. W. Warnhoff, C. M. Wong, and W. T. Tai, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. S-120.
(8) P. E. Eaton and T. W. Cole, Jr., *J. Amer. Chem. Soc.*, **86**, 962, 3157 (1964).
(9) A. Kirmann and H. J. Joschek, *Bull, Soc. Chim. Fr.*, 2483 (1963).
(10) C. L. Stevens, R. D. Elliot, and B. L. Winch, *J. Amer. Chem. Soc.*, **85**, 1464 (1963).
(11) R. D. Kleene, *J. Amer. Chem. Soc.*, **63**, 3538 (1941).
(12) G. Cauquil and J. Rouzand, *C. R. Acad. Sci.*, **237**, 1720 (1953).
(13) C. L. Stevens, A. Thuillier, K. G. Taylor, F. A. Daniher, J. P. Dickerson, H. T. Hanson, N. A. Nielsen, N. A. Tikotkar, and R. M. Weier, *J. Org. Chem.*, **31**, 2601 (1966).
(14) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 787.
(15) C. H. Tilford and M. G. VanCampen, Jr., *J. Amer. Chem. Soc.*, **76**, 2431 (1954), reported the preparation of this ketone in 31% yield from cycloheptylmagnesium bromide and benzonitrile.
(16) S. A. Miller and W. O. Jones, British Patent 738,992 (1955); *Chem. Abstr.* **50**, 10768*f* (1956).
(17) T. A. Favorskaya and I. P. Yakovlev, *Zh. Obshch. Khim.*, **22**, 122 (1952); *Chem. Abstr.*, **46**, 11119*g* (1952).
(18) F. H. Case, *J. Amer. Chem. Soc.*, **56**, 715 (1934).
(19) J. W. Wilt and D. D. Roberts, *J. Org. Chem.*, 27, 3434 (1962); J. W. Wilt, J. F. Zawadzki, and D. G. Schultenover, *ibid.*, **31**, 876 (1966).
(20) C. L. Stevens, T. A. Treat, and P. M. Pillai, *J. Org. Chem.*, **37**, 2091 (1972).
(21) E. E. Smissman and G. Hite, *J. Amer. Chem. Soc.*, **82**, 3375 (1960); E. E. Smissman and J. L. Diebold, *J. Org. Chem.*, **30**, 4005 (1965).
(22) K. Aider, W. Gunzl, and K. Wolf, *Chem. Ber.*, **93**, 809 (1960).

The Selenium Analogs of Biuret

T. Scott Griffin and Daniel L. Klayman*

Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Washington, D. C. 20012

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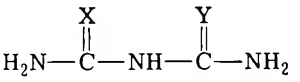
Although the sulfur analogs of biuret (**1**), namely 2-thiobiuret (**2**)[1] and 2,4-dithiobiuret (**3**),[2] were prepared in 1886 and 1945, respectively, the only selenium analog of **1** which is known is 2-seleno-4-thiobiuret (**4**),[3] the synthesis of which was reported comparatively recently from this labo-

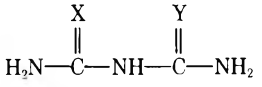
Table I
^{1}H Nmr Chemical Shifts at 60 MHz of Biuret Analogs[a]



Compd	δ, –NH	δ, –C(=X)–NH$_2$	δ, –C(=Y)–NH$_2$
1, X = Y = O	8.67 (s)	6.85 (s)	*b*
2, X = S; Y = O	8.72 (br s)	9.52 (br s), 9.77 (s)[c]	6.58 (s)
3, X = Y = S	11.00 (s)	9.37 (br s)	9.83 (br s)
4, X = Se; Y = S	9.90 (br s)	10.85 (s)	8.95 (br s), 9.03 (br s)[c]
5, X = Se; Y = O	9.45 (br s)	10.00 (br s)	6.67 (br s)
6, X = Y = Se	11.60 (br s)	10.33 (br s)	10.70 (br s)

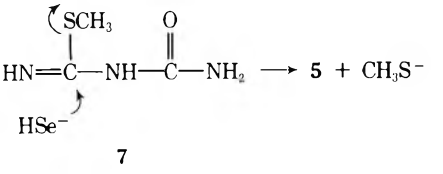
[a] All spectra were measured in DMSO-d_6 using TMS as an internal standard except that of **6**, in which TMS was used as an external standard. [b] The four –NH$_2$ protons are equivalent. [c] Each of the two –NH$_2$ protons is nonequivalent.

ratory. We report here the preparation of the remaining two possible selenium analogs of **1**, *i.e.*, 2-selenobiuret (**5**) and 2,4-diselenobiuret (**6**).



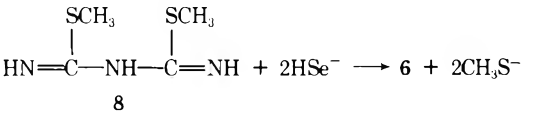
1, X = Y = O
2, X = S; Y = O
3, X = Y = S
4, X = Se; Y = S
5, X = Se; Y = O
6, X = Y = Se

The first, 2-selenobiuret (**5**), was prepared from 2-thiobiuret (**2**) *via* its S-methylated derivative (**7**), which was treated with sodium hydrogen selenide, causing displacement of the methylthio group by the hydrogen selenide anion.[4]



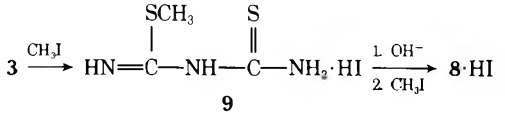
7

2,4-Diselenobiuret (**6**) was synthesized from 2,4-dimethyl-2,4-dithiopseudobiuret (**8**) by treatment with 2.5 equiv of sodium hydrogen selenide, causing displacement of both methylthio groups.



8

2,4-Dimethyl-2,4-dithiopseudobiuret (**8**) was derived from 2,4-dithiobiuret (**3**) by a stepwise S,S-dimethylation with iodomethane to give the hydriodide of **8**.

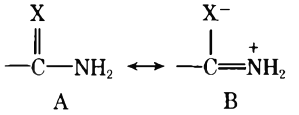


9

The sodium hydrogen selenide utilized in the preparation of **6** was generated conveniently in anhydrous ethanol from 2.5 equiv of selenium and 2.5 equiv of sodium borohydride, a procedure recently reported by us.[5] However, this simplified method for the formation of sodium hydrogen selenide was not used in the synthesis of 2-selenobiuret (**5**) because the water-solubility characteristics of **5** and of the by-product of the selenium–borohydride reaction, namely boric acid, were sufficiently similar to cause difficulties in the isolation of **5**. Therefore, in this case the sodium hydrogen selenide was formed by passing gaseous hydrogen selenide[6] into an aqueous ethanolic solution of sodium bicarbonate.

The monoseleno analogs of biuret, *i.e.*, **4** and **5**, are white or off-white compounds, whereas the diseleno analog **6** is yellow. All of the selenium analogs of biuret are air sensitive, the last being the most sensitive of the three. As with selenoureas,[3] the presence of the selenocarbonyl group was confirmed by the precipitation of red elemental selenium from an ethanolic solution of a selenobiuret to which 1–2 drops of 5% hydrogen peroxide had been added.

Nmr Spectra of Selenobiurets. The imidic –NH protons of the selenium analogs of biuret can be assigned on the basis of integration of peak areas. Using biuret (**1**), 2,4-dithiobiuret (**3**), and 2,4-diselenobiuret (**6**) as models, the chemical shifts of the –CONH$_2$, –CSNH$_2$, and –CSeNH$_2$ protons may be seen to appear in the ranges δ 6–7, 9–10, and 10–11, respectively (Table I). Therefore, in 2-seleno-4-thiobiuret (**4**), the peaks at about δ 9.00 are assigned to –CSNH$_2$ and the peak at δ 10.85 to –CSeNH$_2$. In 2-selenobiuret (**5**), the peak at δ 6.67 is attributed to –CONH$_2$ and that at δ 10.00 to –CSeNH$_2$. Also consistent are the chemical shifts in 2-thiobiuret (**2**), where the singlet at δ 6.58 is due to –CONH$_2$ and the two singlets at δ 9.52 and 9.77 to the nonequivalent –CSNH$_2$ protons. There is clear evidence of increased deshielding of the –CXNH$_2$ protons as X varies from oxygen to sulfur to selenium. This phenomenon may be attributed to decreased electron density on nitrogen, indicating a greater contribution from resonance structure B, which has a positive charge on nitrogen. In



A B

agreement with this postulate, Shine[7] has recently summarized evidence indicating that there is a decreased tendency to form a C=X double bond in amides as X goes from oxygen to sulfur to selenium.

The nonequivalence of the –NH$_2$ groups at room temperature in 2,4-diselenobiuret (**6**) suggests hindered rotation about the internal C–N bonds. Magnetic nonequivalence of groups attached to nitrogen has been detected by nmr

studies and has been attributed to hindered rotation about the C–N bond in selenoamides[8,9] and in selenoureas.[10] As the heteroatom X ranges from oxygen to selenium, the barriers to rotation in amides, $RCXNR'_2$, were observed to increase in the same order.[8,9,11] The barriers to rotation in thiourea and in selenourea, which are similar in value, were found to be greater than seen in urea.[10] The results obtained by us (Table I) are consistent with the effects alluded to above, since the four $-NH_2$ protons in biuret (1) appear as a singlet, whereas in 2,4-dithiobiuret (3) and in 2,4-diselenobiuret (6) the two sets of $-NH_2$ peaks appear separated. In 2-thiobiuret (2) and, to some extent in 2-seleno-4-thiobiuret (4), each of the $-CSNH_2$ protons appear separated as broadened singlets, indicating nonequivalence and hindered rotation about the external C(S)–N bond. This effect would be expected to be operative in the other analogs in the series but is apparently not observable owing to nitrogen quadrupole broadening.

Experimental Section

Unless otherwise indicated, melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were performed by Mr. Joseph F. Alicino, New Hope, Pa., and by Dr. Harry Agahigian of the Baron Consulting Co., Orange, Conn. Infrared spectra were determined in KBr on a Beckman IR-5 spectrophotometer. Nmr spectra were taken in DMSO-d_6 on a Varian A-60 using TMS as an internal standard unless otherwise indicated. Mass spectra were obtained on a Hewlett-Packard 5390A quadrupole mass spectrometer at 70 eV with sample introduction *via* a variably heated direct insertion probe.[12] For the selenium-containing ions, only those peaks corresponding to the most abundant selenium isotope, *i.e.*, 80, are reported. In all cases, the relative intensity patterns of the molecular ion clusters compare favorably with those expected from the selenium natural abundances.[13]

To prevent oxidation, all selenium-containing products were handled in an inert atmosphere.

2-Seleno-4-thiobiuret (4). This compound was prepared by a procedure similar to that previously reported.[3] However, an improvement in the method of generating the sodium hydrogen selenide resulted in doubling the yield of **4.**

To a solution of sodium hydrogen selenide (0.015 mol), obtained from 1.16 g (0.015 mol) of selenium and 0.62 g (0.016 mol) of sodium borohydride in 75 ml of ethanol under argon,[5] was added 2.0 g (0.013 mol) of 2-methyl-2,4-dithiopseudobiuret (**9**) (free base) in 150 ml of ethanol. Stirring and heating at 45° was continued for *ca.* 14 hr until evolution of methyl mercaptan ceased. After cooling the solution to room temperature, 40 ml of deoxygenated water was added followed by a dropwise addition of 3 *N* hydrochloric acid until the pH was about 5. The mixture was purged with argon to remove excess hydrogen selenide which was trapped in a 5% aqueous lead acetate solution. The elemental selenium present in the mixture was removed by filtration and the filtrate was concentrated to about 40 ml. 2-Seleno-4-thiobiuret (1.0 g, 41%), separated at room temperature as tiny, white needles with a pink tinge: mp 171–174° dec (capillary, Thomas-Hoover melting point apparatus); ir (KBr) 3135 (broad, NH), 1615 and 1550 cm^{-1} (amide II); nmr (DMSO-d_6) δ 10.85 (2), 9.90 (1), 9.03 (1), 8.85 (1), all broadened singlets; mass spectrum (70 eV) *m/e* (rel intensity) 183 ($M\cdot^+$, 66), 156 (20), 135 (35), 124 (18), 103 (36), 80 (14), 76 (18), 60 (62), 43 (100). The infrared spectrum of 4 was identical with that of an authentic sample.

2-Selenobiuret (5). Sodium hydrogen selenide solution, prepared by passing hydrogen selenide[6] into 8.2 g (0.1 mol) of sodium bicarbonate dissolved in 100 ml of ethanol and 300 ml of water at 0°, was added to a solution of 13.05 g (0.05 mol) of 2-methyl-2-thiopseudobiuret (**7**) hydriodide in 35 ml of ethanol. This was immediately followed by the addition of 4.2 g (0.05 mol) of sodium bicarbonate in 20 ml of water. When the evolution of carbon dioxide ceased, the flask was stoppered and allowed to stand at room temperature for *ca.* 15 hr. The solution was then purged with nitrogen to remove methyl mercaptan, acidified with glacial acetic acid, and concentrated, causing separation of 6.9 g (83%) of 2-selenobiuret (**5**) as a cream-colored solid. The analytical sample was recrystallized in an argon atmosphere from chloroform–acetonitrile to give white crystals which sublimed and then melted at 185–187° dec: ir (KBr) 3400, 3165 (NH), 1695, 1675 (amide I), and 1597, 1525 cm^{-1} (amide II); nmr (DMSO-d_6) δ 10.00 (2), 9.45 (1), 6.67 (2), all broadened singlets; mass spectrum (70 eV) *m/e* (rel intensity) 167 ($M\cdot^+$, 70), 124 (30), 80 (14), 43 (100).

Anal. Calcd for $C_2H_5N_3OSe$: C, 14.47; H, 3.04; N, 25.31; Se, 47.56. Found: C, 14.53; H, 3.05; N, 25.22; Se, 47.73.

2,4-Diselenobiuret (6). To a solution of sodium hydrogen selenide (0.026 mol), prepared as previously described[5] from 2.04 g (0.026 mol) of selenium and 1.08 g (0.028 mol) of sodium borohydride in 80 ml of ethanol under argon, was added 2,4-dimethyl-2,4-dithiopseudobiuret (**8**) (free base) in 30 ml of ethanol. The reaction mixture was stirred and heated at 50° for 20 hr until evolution of methyl mercaptan virtually ceased. The solution was acidified with 30 ml of deoxygenated hydrochloric acid and purged with argon to remove excess hydrogen selenide which was trapped. The reaction mixture was filtered to remove the trace of Se which separated, concentrated to about 30 ml, and cooled, causing separation of 1.5 g (63%) of 2,4-diselenobiuret (**6**) as a yellow, crystalline material which was analytically pure: mp 165° dec; ir (KBr) 3120 (NH) and 1610, 1540 cm^{-1} (amide II); nmr (DMSO-d_6, external TMS) δ 11.60 (1), 10.70 (2), 10.33 (2), all broadened singlets; mass spectrum (70 eV) *m/e* (rel intensity) 231 ($M\cdot^+$, 9), 124 (62), and 80. The *m/e* 124 peak was observed to intensify with increasing sample time in the probe, suggesting possible thermal decomposition of **6.**

Anal. Calcd for $C_2H_5N_3Se_2$: C, 10.49; H, 2.20; N, 18.35; Se, 68.96. Found: C, 10.49; H, 2.13; N, 18.20; Se, 68.77.

2,4-Dimethyl-2,4-dithiopseudobiuret (8) Hydriodide. To 10.4 g (0.037 mol) of 2-methyl-2,4-dithiopseudobiuret (**9**) hydriodide[3] dissolved in 90 ml of water was added slowly 3.1 g (0.037 mol) of sodium bicarbonate in 24 ml of water. The thick white precipitate which formed was collected, suspended in acetonitrile, and treated with 8.5 g (0.06 mol) of iodomethane. The mixture was heated under reflux for 1 hr and concentrated, causing separation of 7.7 g (72% of 2,4-dimethyl-2,4-dithiopseudobiuret (**8**) hydriodide as cream-colored crystals which were analytically pure: mp 170–171° dec; ir (KBr) 3225 (NH), 3096 (CH), 1613 (C=N), and 1567 cm^{-1} (NH).

Anal. Calcd for $C_4H_{10}N_3S_2I$: C, 16.50; H, 3.46; N, 14.43; S, 22.02; I, 43.58. Found: C, 16.36; H, 3.38; N, 14.44; S, 21.94; I, 43.26.

2,4-Dimethyl-2,4-dithiopseudobiuret (8) was prepared by suspending 1.5 g (0.005 mol) of 8 hydriodide in 20 ml of chloroform followed by the addition of 1.0 g (0.007 mol) of potassium carbonate in 20 ml of water. After the two phases were stirred for 15 min, the chloroform layer was separated, dried, and evaporated, yielding a colorless oil which crystallized upon standing. The 2,4-dimethyl-2,4-dithiopseudobiuret (**8**), after washing with hexane, was analytically pure, mp 92–93°. The compound has a strong odor of methyl mercaptan indicative of slow decomposition and was generally used immediately after preparation.

Anal. Calcd for $C_4H_9N_3S_2$: C, 29.43; H, 5.56; N, 25.74; S, 39.28. Found: C, 29.38; H, 5.68; N, 25.72; S, 38.72.

Registry No.—**1,** 108-19-0; **2,** 23228-74-2; **3,** 541-53-7; **4,** 21347-30-8; **5,** 52216-82-7; **6,** 52175-64-1; **7** HI, 34277-75-3; **8,** 15013-75-9; **8** HI, 52175-65-2; **9,** 40056-40-4; **9** HI, 21347-31-9; sodium hydrogen selenide, 12195-50-5.

References and Notes

(1) A. Wunderlich, *Ber.*, **19,** 449 (1886).
(2) R. L. Sperry, U. S. Patent 2,371,112 (March 6, 1945). See also F. Kurzer, "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 502.
(3) D. L. Klayman and R. J. Shine, *J. Org. Chem.*, **34,** 3549 (1969).
(4) We thank Dr. Thomas E. Fink for performing the initial studies on the preparation of **5.**
(5) D. L. Klayman and T. S. Griffin, *J. Amer. Chem. Soc.*, **95,** 197 (1973).
(6) Hydrogen selenide was generated from aluminum selenide by addition of dilute sulfuric acid in a manner described by F. Bennett and R. Zingaro, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 359.
(7) R. J. Shine, "Organic Selenium Compounds: Their Chemistry and Biology," D. L. Klayman and W. H. H. Günther, Ed., Wiley, New York, N. Y., 1973, p 280.
(8) G. Schwenker and H. Rosswag, *Tetrahedron Lett.*, 4237 (1967).
(9) K. A. Jensen and J. Sandström, *Acta Chem. Scand.*, **23,** 1911 (1969).
(10) W. Walter, E. Schaumann, and H. Rose, *Tetrahedron*, **28,** 3233 (1972).
(11) R. C. Neuman, Jr., D. N. Roark, and V. Jonas, *J. Amer. Chem. Soc.*, **89,** 3412 (1967).
(12) We are grateful to Dr. James A. Kelley for the mass spectra.
(13) L.-B. Agenäs in ref 7, p 964.

The Effect of Ortho-Alkyl Substituents in the Metalation Reactions of Substituted Anisoles

Thomas E. Harmon* and David A. Shirley

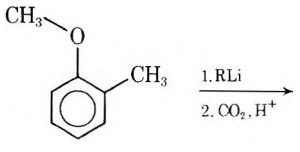
Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37916

Received February 15, 1974

In order to determine the role played by oxygen coordination in the metalation of anisole, Slocum and Koonsvitsky[1] recently investigated the lithiation of *o-tert*-butylanisole (**1**). Metalation of **1** with *n*-butyllithium in ether solvent gave only a 7.5% yield upon carbonation, whereas anisole[2] itself gave a 65% yield of ortho metalation under similar conditions. When 1 equiv of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was added, a 30% yield of ortho metalation of **1** was observed. These results were attributed to the steric interference of the *tert*-butyl group reducing the possibility for *n*-butyllithium coordination with the ether oxygen of **1** compared to that with anisole. The higher yield of metalation with *n*-butyllithium–TMEDA was attributed to the higher reactivity of this reagent.

Results and Discussion

Recent investigations in this laboratory do not support the above conclusions. The metalation of a similar substrate, *o*-methylanisole (**2**), has been studied in hydrocarbon solvent under various conditions and compared to similar metalations of anisole. Letsinger and Schnizer[3] previously studied the metalation of **2** with *n*-butyllithium. These workers isolated the carboxylic acid products by fractional crystallization and reported the products to consist of approximately equal amounts of **3** and **4**. The same



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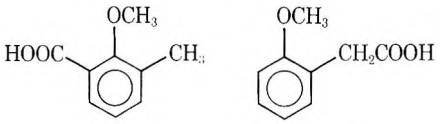


3 **4**

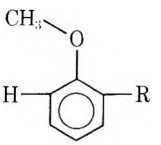
products were obtained in our investigations but the relative percentages of each varied according to the reaction conditions The product distribution was determined in each case by gas chromatographic analysis of the corresponding methyl esters.

Metalation of **2** with *n*-butyllithium in refluxing cyclohexane for 10 hr followed by carbonation gave a 57% yield of carboxylic acid products. Analysis of the product composition revealed that one-third of these products, or 19%, resulted from ortho metalation. Under similar conditions, anisole was converted to the ortho acid in 40% yield. When **2** was metalated with *tert*-butyllithium for 10 hr in refluxing cyclohexane–pentane, an 81% yield was found of which 34% was ortho metalation product. Anisole was metalated under similar conditions to give a 51% yield of ortho metalation[4] product. When the metalation of **2** was carried out for 10 hr at room temperature with *n*-butyllithium–TMEDA in cyclohexane solvent, a 72% yield of acidic product was obtained including 54% of the ortho metalation product. Anisole was metalated to give only 54% yield of the ortho acid with *n*-butyllithium–TMEDA under these conditions.[5]

In order to compare the relative amounts of ortho metalation obtained in the reactions with anisole and **2** as indicated above, a statistical factor must be applied to the anisole results, since there are two ortho positions available for metalation *vs.* one ortho position in **2**. Therefore metalation of anisole with *n*-butyllithium, *tert*-butyllithium, and *n*-butyllithium–TMEDA resulted in 20, 26, and 27% yields of metalation per ortho position compared to the 19, 34, and 54% yields of ortho metalation observed with **2**. These results indicate that the methyl group does not reduce the ortho metalation reactivity of **2** compared with anisole and that any steric hindrance to alkyllithium coordination in **2** is not an important factor.

Complexation of *n*-butyllithium with donor molecules has been shown to produce an upfield shift in the nmr signal of the α-methylene protons of *n*-butyllithium. The magnitude of these shifts is taken as a measure of the degree of complexation. Thus, the coordination of ethyl ether and *n*-butyllithium in hexane produced a 9.0-Hz upfield shift for the methylene protons α to lithium.[6] Ellison and Kotsonis[7] obtained evidence for a 1:1 complex with anisole and *n*-butyllithium by observing a maximum upfield shift of 4.0 Hz at this mole ratio. The metalation of **1** was carried out by Slocum and Koonsvitsky[1] in ethyl ether solvent, as was the metalation of anisole[2] to which they referred. In such an excess of ether, it appears unlikely that complexation of *n*-butyllithium with **1** or anisole would be important in determining the rate and yield of metalation of these substrates. Certainly when TMEDA[8] is present, very little if any complexation of the *n*-butyllithium with the anisole substrate occurs. The above authors correctly stated that the reactive *n*-butyllithium–TMEDA species need not form a complex with oxygen of **1** to effect metalation.

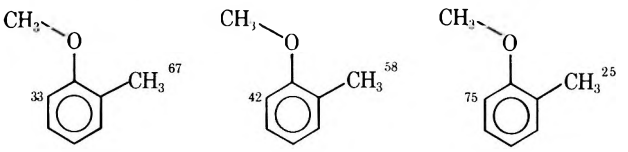
A recent investigation[9] of the metalation of 3-alkyl- and 3,5-dialkylanisoles as well as other substrates has pointed to the importance of the oligomer size of the attacking alkyllithium species and the steric environment of the ortho hydrogens of each substrate in determining the yield and position of metalation. We believe that the results of Slocum and Koonsvitsky[1] can be interpreted using these same concepts. In hydrocarbon solvent *n*-butyllithium is known to be hexameric[10] and *n*-butyllithium–TMEDA is monomeric.[8] *n*-Butyllithium exists as a tetramer[10] in ethyl ether. It is reasonable to assume that the steric requirement of the reactive *n*-butyllithium oligomer is greater than that of the *n*-butyllithium–TMEDA monomer. Owing to the steric effect of the *o-tert*-butyl group, the conformation of **1** would be fixed as shown in **5**. The large *n*-butyllithium oligomer would be sterically hindered from attacking the ortho hydrogen of **5**, whereas no such steric interference would occur with anisole. This steric effect plus the deactivating inductive effect[11] of the *tert*-butyl group would account for the rate and yield difference in the metalation of these substrates noted by Slocum and Koonsvitsky.[1] Furthermore, in the metalation of **1** with the monomeric *n*-butyllithium–TMEDA, the lower steric requirement of this metalation reagent would be expected to lead to a higher yield as was observed.[1]



5, R = *tert*-butyl
6, R = methyl

* E. I. du Pont de Nemours and Co., Chattanooga, Tenn. 37401.

Interesting product distribution shifts were observed in the above metalations of **2** with *n*-butyllithium, *tert*-butyllithium, and *n*-butyllithium–TMEDA as indicated below.



n-BuLi *t*-BuLi *n*-BuLi–TMEDA

The numbers indicate the percentage of total metalation observed at each position. These results are also explainable in terms of the steric environment of the ortho hydrogens and the oligomer size of the alkyllithium reagent. The expected stable conformation of **2** would also be **6**.[12] Since *tert*-butyllithium is tetrameric[10] in hydrocarbon, the oligomer size of the metalation reagents would be expected to decrease in the order *n*-BuLi > *t*-BuLi > *n*-BuLi–TMEDA. The product distributions observed in these metalation reactions of **2** are consistent with the concept of the alkyllithium reagent with the least steric requirement effecting the largest amount of metalation at the hindered ortho position.

These product distribution results may also be rationalized in terms of the base strength of the reagents, which increases in the order *n*-BuLi < *t*-BuLi < *n*-BuLi–TMEDA.[8,13] A correlation is observed which indicates that the ratio of ring to lateral metalation increases with the base strength of the metalation reagent. The same conclusion was reached by Broaddus[5] concerning the metalation of toluene with *n*-butyllithium–TMEDA. He believed that the metalation reaction was controlled by proton abstraction processes and compared his data to the results of base-catalyzed isotopic exchange reactions of toluene. These results revealed a decreasing reactivity of benzylic positions relative to ring positions with increasing base strength. Broaddus rationalized his results in terms of the principle[14] that the C–H bond will be broken to the largest extent in the transition state involving the weakest base. Therefore, it may be reasonably proposed that electron delocalization stabilizing factors will also be largest with the weakest base. When more charge is developed on carbon, delocalization is a more important factor and thus reaction is favored at benzylic positions relative to ring positions.[5]

In any case the degree of complexation of the alkyllithium reagent with the oxygen of **2** does not appear to be the predominant factor in determining the yield or position of metalation. This argument seems even clearer for the metalations of anisole[2] and **1**[1] in ether solvent, where the coordination between *n*-butyllithium and the anisole substrates would be negligible based on the cited nmr data.[6,7]

Experimental Section

A. General Considerations. Solutions of *n*-BuLi in cyclohexane and *t*-BuLi in pentane were obtained from Foote Mineral Co. The concentration of the organolithium reagents used was determined by the method of Gilman and Cartledge.[15] Cyclohexane was refluxed for several hours over lithium aluminum hydride, distilled, and stored over freshly cut sodium. TMEDA (Aldrich Chemical Co.) was distilled from $LiAlH_4$ and stored over Linde MS-4A molecular sieve. *o*-Cresol was obtained from Eastman Chemical Co. and used without further purification.

B. Metalation of *o*-Methylanisole. *o*-Methylanisole was prepared from *o*-cresol with sodium hydroxide and dimethyl sulfate using the standard procedure.[16] Following fractional distillation *in vacuo* no impurities were detected by gc analysis and an nmr spectrum was consistent with expectation.

The general apparatus and procedure for the metalation reactions, carbonation, and conversion of the products to their methyl esters has been previously described.[9] The product methyl esters were analyzed on a Varian Aerograph 711 using an FFAP column at 210° and a carrier gas flow rate of 400 cc/min. All of the chromatograms exhibited two peaks with retention times of 22.3 and 29.1 min which varied in size according to the reaction conditions. The components responsible for these peaks were isolated by preparative scale gc and identified by their nmr spectra. The nmr spectrum of the component with the retention time of 22.3 min showed a singlet of three protons at δ 2.28, a singlet of three protons at δ 3.77, a singlet of three protons at δ 3.84, and a complex multiplet of three protons at δ 6.74–7.65. This spectrum is clearly representative of methyl 2-methoxy-3-methylbenzoate, the product of metalation ortho to the methoxy group. The nmr spectrum of the component appearing at 29.1 min exhibited a singlet of two protons at δ 3.54, a singlet of three protons at δ 3.62, a singlet of three protons at δ 3.79, and a complex multiplet of four protons at δ 6.62–7.36. This spectrum is interpretable only for methyl *o*-methoxyphenylacetate, the product of metalation of the methyl group.

The product composition of these reactions was determined by the relative peak areas of the chromatograms as measured by a Disc integrator.

Registry No.—**2**, 578-58-5; **3** methyl ester, 52239-62-0; **4** methyl ester, 27798-60-3.

References and Notes

(1) D. W. Slocum and B. P. Koonsvitsky, *J. Org. Chem.*, **38**, 1675 (1973).
(2) D. A. Shirley, J. R. Johnson, Jr., and J. P. Hendrix, *J. Organometal. Chem.*, **11**, 209 (1968).
(3) R. L. Letsinger and A. W. Schnizer, *J. Org. Chem.*, **16**, 869 (1951).
(4) D. A. Shirley and J. P. Hendrix, *J. Organometal. Chem.*, **11**, 217 (1968).
(5) C. D. Broaddus, *J. Org. Chem.*, **35**, 10 (1970).
(6) Z. K. Cheema, G. W. Gibson, and J. F. Eastham, *J. Amer. Chem. Soc.*, **85**, 3517 (1963).
(7) R. A. Ellison and F. N. Kotsonis, *Tetrahedron*, **29**, 805 (1973).
(8) A. W. Langer, Jr., *Trans. N. Y. Acad. Sci.*, **27**, 741 (1965).
(9) D. A. Shirley, T. E. Harmon, and C. F. Cheng, *J. Organometal Chem.*, **69**, 327 (1974).
(10) H. L. Lewis and T. L. Brown, *J. Amer. Chem. Soc.*, **92**, 4664 (1970).
(11) D. A. Shirley and E. A. Lehto, *J. Amer. Chem. Soc.*, **79**, 3481 (1957).
(12) N. L. Allinger, *J. Org. Chem.*, **36**, 2747 (1971).
(13) D. E. Applequist and D. F. O'Brien, *J. Amer. Chem. Soc.*, **85**, 743 (1963).
(14) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 158.
(15) H. Gilman and F. K. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964).
(16) H. Gilman, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1964, p 58.

2,6-Dinitro-*N*-(2-imidazolyl)-*p*-toluidine

John C. Grivas* and Krishna C. Navada

Chicago Chemicals Laboratory, Sherwin Williams Chemicals, The Sherwin-Williams Company, Chicago, Illinois 60628

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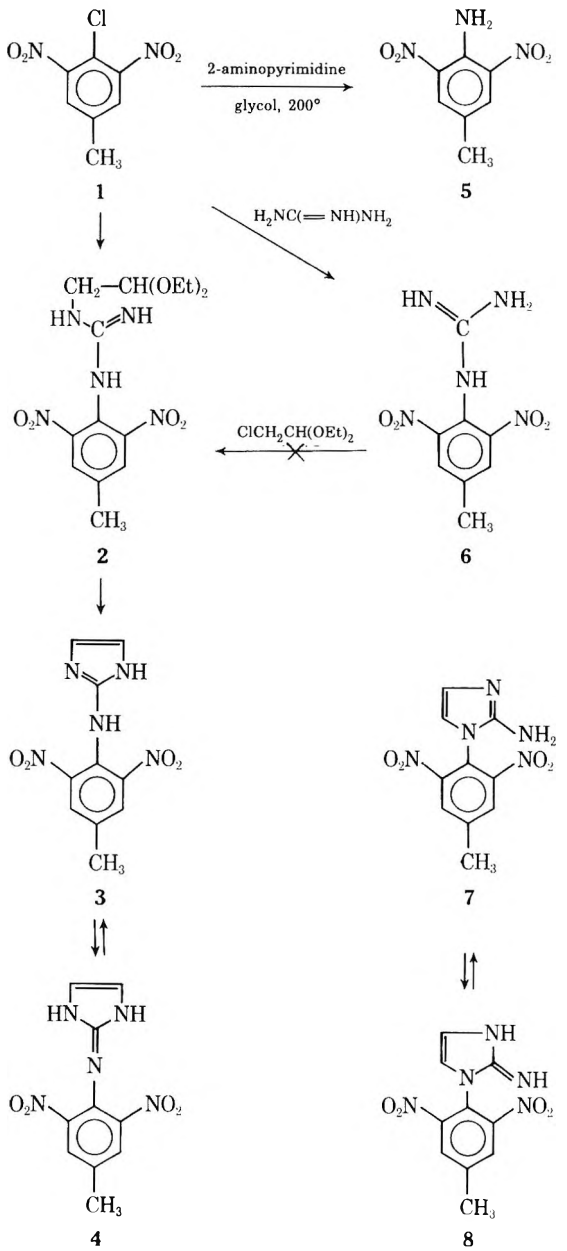
During the course of other work it became necessary to prepare 2,6-dinitro-*N*-(2-imidazolyl)-*p*-toluidine (**3**) for biological screening. This preparation could not be achieved by the direct displacement of chloride ion from 4-chloro-3,5-dinitrotoluene (**1**) by 2-aminoimidazole. Although such a displacement by aliphatic and aromatic amines[1,2] as well as alkoxide ions[3] is well known, our initial few attempts to condense **1** with 2-aminoimidazole, and another more stable heterocyclic amine, were not successful. For example, heating **1** with 2-aminoimidazole in dimethylformamide at 135° for 7 hr gave an intractable mixture of at least four major components. On the other hand, when the same reactants were heated under reflux in ethanol for 8 hr, nearly all **1** was recovered unchanged. Treating **1** with 2-aminopyrimidine (1:2 molar ratio) in glycol at 135° for 24 hr resulted in little change. Unexpectedly, at higher temperatures **1** reacted completely to afford 2,6-dinitro-*p*-toluidine (**1** → **5**) and a substantial amount of tar. A possible

course of this reaction was subsequently traced to an attack of glycol on 2-aminopyrimidine accompanied by evolution of ammonia. The latter reacted with **1** to give **5**. The reaction of **1** with heterocyclic amines was not investigated further. A second route toward **3** (**1** → **6** → **2** → **3**) was also abandoned because **6** could not be converted to **2** by alkylation with chloroacetaldehyde diethyl acetal.



The synthesis of **3** was then achieved by building up the imidazole moiety in the following manner. Heating *N*-(2,2-diethoxyethyl) guanidine[4] with **1** in methanol gave **2** (61%) along with a lesser amount of 3,5-dinitro-4-methoxytoluene from the reaction of **1** with the solvent. The nmr spectrum of **2** was in accord with the assigned structure. The signals for the adjacent CH_2 and NH protons appeared as triplets at 3.28 and 6.16 ppm, respectively, while those of the other two NH protons formed a sharp singlet at 5.78 ppm. Upon deuteration all NH peaks exchanged, and the methylene triplet collapsed into a doublet, establishing firmly the NH positions and those of the aliphatic portion of the molecule.

Ring closure of **2** was carried out in concentrated hydrochloric acid[5] to yield a yellow substance which, conceivably, could be one of two products from two different reaction paths. According to one of the possible paths, the aldehyde moiety generated through acidic hydrolysis condenses with the imino group of **2** to give **3**. Alternatively, condensation with the secondary aromatic NH leads to the isomeric structure **7**. In addition, structures **3** and **7** could exist in the form of their tautomeric counterparts **4** and **8**. Ir spectra did not permit an unambiguous distinction among the four possible structures. Thus, dilute solutions of the condensation product in chloroform showed two peaks of medium intensity at 3430 and 3250 cm^{-1}, respectively. These could be attributed to the ν_{as} and ν_s modes of the primary amine group of **7** or the two secondary ν(NH) vibrations of the imidazole[6] and amino groups of **3**. Intramolecular hydrogen bondings between NH and NO_2 and the imidazole ring polymers[6] were also evident because the lower frequency band was rather broad with shoulders. Structures **4** and **8** are not consistent with the absorption at 3430 cm^{-1}, since they possess only secondary NH groups and are devoid of the imidazole aromatic ring. Convincing evidence against **7** and **8** and in support of **3** was provided by the nmr spectrum of the cyclization product, which in addition to the methyl frequency at 2.4 ppm exhibited only two very sharp signals in the aromatic region. The signal at 8.1 ppm was assigned to the phenyl protons in agreement with the same signals at 7.88 and 7.84 ppm for **2** and **6**, respectively. The second sharp signal at 6.67 ppm is in accord with the magnetic equivalency[7] of the two CH protons of the imidazole ring of **3**. Although the peaks for the two NH protons of **3** were too broad to be detected,[8] deuteration confirmed the presence of the two exchangeable hydrogens. Structures **7** and **8** were excluded on the basis that their imidazole CH protons are nonequivalent and should exhibit two signals[9] instead of the observed one. Consequently, structure **3** was assigned to the ring closure product.

Finally, evidence against a completely planar **3** was found in the uv–visible spectra of **2**, **3**, **5**, and **6**, which showed that considerable changes of the higher wavelength absorption occurred. Compound **5** absorbed at 438 nm, whereas **2** and **6** absorbed at 349 and 343 nm for a hypsochromic shift of 89 and 85 nm, respectively. The ϵ value also decreased by approximately 70%, from 7300 for **5** to 2400 for **2**. These significant changes of λ_{max} and ϵ in going from an amino to a guanidino group are indicative of the substantial decrease in overlap between the phenyl π electrons and the lone pair of the nitrogen atom adjacent to it. The "freeze" of this nitrogen electron pair should be due to its engagement into resonance within the quanidino moiety, which is opposed to the resonance with the phenyl ring. With the formation of the imidazole ring (**3**), the resonance within the guanidino group is suppressed, since two of its nitrogen atoms now participate in the resonance of the imidazole ring. Actually, the two rings and the connecting nitrogen should be expected to interact[2] and compound **3** should absorb at a wavelength higher than 438 nm. The fact that **3** absorbed at 411 nm can be attributed to steric hindrance which forces the two rings at an angle with respect to each other. In a similar structure, *N*-picryl-*p*-iodoaniline for example, the two aryl groups have been reported[10] to be tilted by 65° relative to each other.

Experimental Section[11]

***N*-(2,2-Diethoxyethyl)guanidine Sulfate.** The compound was prepared as described previously[4] in 80% yield, mp 154–156° (lit.[4] mp 148–152°).

***N*-(2,2-Diethoxyethyl)-*N'*-(2,6-dinitro-4-methylphenyl)-guanidine (2).** To a solution of sodium hydroxide (2 g, 0.05 mol) in methanol (200 ml), *N*-(2,2-diethoxyethyl)guanidine sulfate (12.3 g, 0.0275 mol) was added and the mixture was stirred for 30 min. After the addition of 3,5-dinitro-4-chlorotoluene (**1**, 5.4 g, 0.025 mol) the reaction mixture was refluxed for 28 hr and filtered, and the filtrate was evaporated to dryness under vacuum to yield an oily residue. The residue was triturated with water (three 30-ml

portions) and crystallized from ethanol to give crude **2** (4 g), which was purified by four recrystallizations from benzene: yellow crystals, mp 139–140°; yield 1.6 g (18%); nmr (DMF-d_6) δ 1.15 (t, 6, OCH_2CH_3), 2.38 (s, 3, aromatic CH_3), 3.28 (t, 2, $HNCH_2CH$), 3.6 (m, 4, OCH_2CH_3), 4.65 (t, 1, $HNCH_2CH$), 5.78 (s, 2, $-C(=NH)NH-$), 6.16 (t, 1, $NHCH_2CH$), 7.88 (s, 2, aromatic H); λ_{max} (MeOH) 218 nm (ϵ 21,000), ~240 sh (15,000), 349 (2400).

Anal. Calcd for $C_{14}H_{21}N_5O_6$: C, 47.32; H, 5.96; N, 19.71; O, 27.01. Found: C, 47.12; H. 5.95; N, 19.69; O, 27.14.

The filtrates from the ethanol and benzene crystallizations were combined and evaporated to dryness under vacuum to yield a gummy residue (7 g) which was dissolved in benzene and chromatographed on alumina. Elutions with benzene gave 1.2 g of 3,5-dinitro-4-methoxytoluene, mp 121–123° (lit.[3] mp 123–124°). Further elutions with benzene and benzene–chloroform solutions of increased polarity yielded additional pure **2** (3.8 g, mp 139–140°). Total yield was 5.4 g (61%).

2,6-Dinitro-*N*-(2-imidazolyl)-*p*-toluidine (3). Intermediate **2** (1.4 g, 4 mmol) in concentrated hydrochloric acid (6.5 ml) was heated on a steam bath for 1 hr. The reaction mixture was diluted with water (25 ml), boiled to remove hydrochloric acid, decolorized with charcoal, cooled, and neutralized with ammonium hydroxide. The precipitated red crude **3** was purified by crystallization from ethanol (mp 219–221°, yield 0.4 g, 39%). An additional recrystallization from ethanol gave pure **3**: mp 220–221.5°; nmr (DMF-d_6) δ 2.4 (s, 3, CH_3), 6.67 (s, 2, imidazole H), 8.1 (s, 2, aromatic H); λ_{max} (MeOH) 241 nm (ϵ 17,500), 411 (4000).

Anal. Calcd for $C_{10}H_9N_5O_4$: C, 45.63; H, 3.45; N, 26.61; O, 24.31. Found: C, 45.61; H, 3.45; N, 26.40; O, 24.08.

3,5-Dinitro-4-guanidinotoluene (6). Guanidine hydrochloride (4.8 g, 0.05 mol) was added to a solution of sodium hydroxide (2 g, 0.05 mol) in methanol (50 ml) at 10–12°. The mixture was stirred for 5 min, the precipitated sodium chloride was filtered off, and the methanolic guanidine so obtained was added to a solution of **1** (5.4 g, 0.025 mol) in methanol (150 ml). The reaction mixture was refluxed for 20 hr, cooled, clarified by gravity filtration, and evaporated to dryness under vacuum to give a semisolid dark residue. The residue was stirred in water (100 ml) for 15 min, filtered off, and recrystallized from acetone–methanol. The crude product obtained was refluxed in benzene (100 ml) for 1 hr, filtered off, and recrystallized from methanol to give pure **5**: mp 235–236°; yield 1.1 g (18%); nmr (DMF-d_6) δ 2.37 (s, 3, CH_3), 5.84 (s, 4, $NHC(=NH)NH_2$), 7.84 (s, 2, aromatic H); λ_{max} (MeOH) 216 nm (ϵ 19,000), ~240 sh (~ 15,000), 343 (2500).

Anal. Calcd for $C_8H_9N_5O_4$: C, 40.17; H, 3.79; N, 29.28. Found: C, 40.08; H, 3.84; N, 29.47.

The aforementioned benzene solution was concentrated and cooled to yield 3,5-dinitro-4-methoxytoluene (2.1 g) formed by the concurrent reaction of **1** with the solvent methanol, mp 123° (lit.[3] mp 123–124°).

Reaction of 4-Chloro-3,5-dinitrotoluene with 2-Aminopyrimidine. 2,6-Dinitro-*p*-toluidine (5). A solution of **1** (54.2 g, 0.25 mol) and 2-aminopyrimidine (52.3 g, 0.55 mol) in glycol (125 ml) was stirred at 195–200° for 3 hr, cooled, and filtered. The black solid obtained was dissolved in acetone (500 ml) and filtered from undissolved tar, and the filtrate was brought to dryness under vacuum to yield an orange solid. This solid was purified by crystallization from methylene chloride–ethanol, mp 167–171°, yield 19.4 g (39%). Two additional recrystallizations from chloroform–methanol and benzene gave pure **5**, mp 170–171° (lit.[12] mp 172°). The compound was identified by ir spectrum and mixture melting point with an authentic sample: λ_{max} (MeOH) 224 nm (ϵ 16,000), 252 (7300), 438 (7300).

Anal. Calcd for $C_7H_7N_3O_4$: N, 21.31. Found: **N**, 21.58.

Registry No.—**1**, 5264-65-3; **2**, 52225-72-6; **3**, 52225-71-5; **5**, 6393-42-6; **6**, 52322-50-6; *N*-(2,2-diethoxyethyl)guanidine sulfate, 52225-73-7; guanidine hydrochloride, 50-01-1; 2-aminopyrimidine, 109-12-6.

References and Notes

(1) W. Borsche and A. Fiedler, *Chem. Ber.*, **46**, 2117 (1913); R. E. Parker and T. O. Reed, *J. Chem. Soc.*, 3149 (1962).
(2) A. T. Balaban, P. T. Frangopol, M. Frangopol, and N. Negoita, *Tetrahedron*, **23**, 4661 (1967).
(3) J. C. Grivas, *J. Org. Chem.*, **38**, 1204 (1973); J. F. Bunnet, H. Moe and D. Knutson, *J. Amer. Chem. Soc.*, **76**, 3936 (1954).
(4) B. T. Storey, W. W. Sullivan, and C. L. Moyer, *J. Org. Chem.*, **29**, 3118 (1964).
(5) A. Lawson, *J. Chem. Soc.*, 307 (1956).
(6) D. M. Anderson, J. L. Duncan, and F. J. C. Rossoti, *J. Chem. Soc.*, 2165 (1961).
(7) S. M. Wang and C. Li, *J. Amer. Chem. Soc.*, **88**, 4592 (1966).
(8) Imidazole does not exhibit NH resonance signal at low concentrations (see ref 7).
(9) G. S. Reddy, R. T. Hobgood, Jr., and J. H. Goldstein, *J. Amer. Chem. Soc.*, **84**, 336 (1962).
(10) E. Grison, *Acta Crystallogr.*, **2**, 410 (1949).
(11) Melting points were determined with a Thomas-Hoover melting point apparatus and were not corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The nmr spectra were recorded on a Varian HA-100 spectrometer using tetramethylsilane as internal reference. Ir spectra were determined with a Perkin-Elmer 221 spectrophotometer. Uv-visible spectra were recorded on a Unicam SP 1700/1800 spectrophotometer.
(12) H. Lindemann and H. Krause, *J. Prakt. Chem.*, **115**, 264 (1927).

Preparation of *cis*-Methyl α-(Tetrahydro-2-furylidene)acetate

Sharon A. Krueger and Thomas A. Bryson*

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

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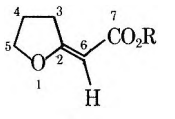
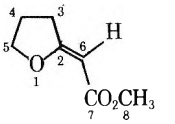
Several methods for the preparation of *trans*-α-(tetrahydro-2-furylidene)acetates **1** have been reported in the literature.[1,2] We wish now to report the successful preparation of the thermodynamically less stable *cis*-methyl α-(tetrahydro-2-furylidene)acetate (**2**) by stereospecific displacement of iodide ion in *trans*-methyl 3-iodo-6-hydroxy-2-hexenoate (**4**).

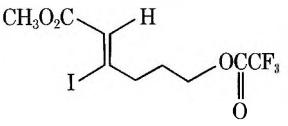


1



2

trans-Methyl 3-iodo-6-hydroxy-2-hexenoate (**4**) was obtained by hydrolysis of *trans*-methyl 3-iodo-6-trifluoroacetoxy-2-hexenoate (**3**)[3] with 1 equiv of potassium carbonate in water–methanol–THF (10:1:2). Treatment of **4** with silver oxide (excess) in ethyl ether gave a 1:1 mixture of the cis isomer **2** and the starting alcohol which could be separated by rapid partial distillation at reduced pressure. However, slow distillation at reduced pressure converts the cis isomer quantitatively into the trans isomer (**1**).[4] At room temperature the cis isomer slowly (several days) isomerizes to **1**. This latter isomerization (**2** to **1**) limited the reaction time that could be used for the conversion of iodide **4** to furylidene **2**. The cis isomer (**2**) could be stored for up to 4 months at −10° without detectable changes in structure.



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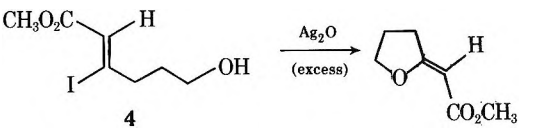

4 **2**

Under more vigorous cyclization conditions the iodo alcohol **4** could be completely converted to a furylidene structure; however, the products thus formed were mixtures of geometric isomers. For example, treatment of **4**

Table I
Spectral Data of *cis*- and *trans*-Methyl α-(Tetrahydro-2-furylidene)acetate

	cis-	*trans*-
Ir, λ_{max} (film)	1702, 1644 cm^{-1}	1701, 1641 cm^{-1}
Pmr, δ_{TMS} (CCl_4)	C-3 H's (2.64, m)	C-3 H's (3.03, m)
	C-4 H's (2.00, m)	C-4 H's (2.02, m)
	C-5 H's (4.30, t, J = 6.5 Hz)	C-5 H's (4.13, t, J = 7 Hz)
	C-6 H (4.64, t, J = 1.2 Hz)	C-6 H (5.11, t, J = 1.5 Hz)
	C-8 H's (3.53, s)	C-8 H's (3.54, s)
Cmr, ppm (TMS, $CDCl_3$)	C-2 (172.26)	C-2 (176.99)
	C-3 (32.18)	C-3 (30.33)
	C-4 (23.28)	C-4 (23.92)
	C-5 (74.42)	C-5 (71.90)
	C-6 (87.79)	C-6 (89.12)
	C-7 (166.41)	C-7 (168.88)
	C-8 (50.62)	C-8 (50.52)

with sodium hydride in THF or sodium methoxide in methanol resulted in the formation of a mixture of cis and trans isomers in ratios of 23:77 and 21:79, respectively. We note also that treatment of the trifluoroacetoxy compound **3** with thallous ethoxide in ethyl ether gave a similar mixture of cis and trans isomers in a ratio of 28:72.

Stereochemical assignments are based on (a) ir, pmr, and cmr data (see Table I), (b) the observed ease of conversion of the cis isomer into the trans isomer, and (c) nmr shift reagent studies using tris(dipivalomethanato)europium(III) or $Eu(DPM)_3$.[1] With $Eu(DPM)_3$ larger deshielding effects were observed for the C-3 hydrogens in the trans isomer **1**, where these allylic hydrogens are close to the carbonyl group, than in the cis isomer **2**, where the corresponding methylene hydrogens are well removed from the carbonyl group.

Experimental Section

Preparation of *trans*-Methyl 3-Iodo-6-hydroxy-2-hexenoate. To a solution of *trans*-methyl 3-iodo-6-trifluoroacetoxy-2-hexenoate (3.66 g, 10 mmol) in 2.5 ml of methanol and 5 ml of tetrahydrofuran was added a solution of potassium carbonate (1.38 g, 10 mmol) in 25 ml of water. The resulting mixture was stirred for 4 hr at room temperature and then extracted with ethyl ether (3 × 25 ml). The combined ether extracts were washed with water (25 ml) and saturated sodium chloride solution and dried (Na_2SO_4). The solvent was removed *in vacuo* to give 2.56 g of a pale yellow oil which was distilled (Kugelrohr oven, 150°, 0.9 mm) to yield 2.48 g (92%) of *trans*-methyl 3-iodo-6-hydroxy-2-hexenoate: λ_{max} (film) 3400, 1720, 1620, 1180 cm^{-1}; pmr δ_{TMS} (CCl_4) 6.37, (s, 1, C-2 H), 3.62 (m, 6, C-6, C-7 H's, OH), 2.80 (m, 2, C-4 H's), 1.78 (m, 2, C-3 H's).

Preparation of *cis*-Methyl α-(Tetrahydro-2-furylidene)acetate. To a suspension of silver oxide (0.765 g, 3.3 mmol) in ethyl ether (10 ml, distilled from sodium) was added *trans*-methyl 3-iodo-6-hydroxy-2-hexenoate (0.81 g, 3 mmol). The mixture was stirred under nitrogen at room temperature overnight and then filtered through a pad of Celite to remove the silver salts. The solvent was removed *in vacuo* to give 0.60 g of a light yellow oil which was a 1:1 mixture of starting material and desired product (determined by nmr). The oil was partially distilled[6] (Kugelrohr oven, 107°, 0.6 mm) and then partially redistilled (Kugelrohr oven, 107° 0.6 mm) to afford a sample of *cis*-methyl α-(tetrahydro-2-furylidene)acetate pure enough for spectral analysis: mass spectrum *m/e* 142 (see Table I for other spectral data).

Acknowledgment. We gratefully acknowledge the support of the American Cancer Society (Grant IC-83).

Registry No.—**1**, 52196-15-3; **2**, 52196-16-4; **3**, 51755-87-4; **4**, 52259-83-3.

References and Notes

(1) T. A. Bryson, *J. Org. Chem.*, **38**, 3428 (1973); see also footnote 5.
(2) F. F. Blick and B. A. Brown, *J. Org. Chem.*, **26**, 3685 (1961).
(3) T. A. Bryson, *Tetrahedron Lett.*, 4923 (1973).
(4) All compounds were analyzed by ir and nmr before and after each distillation.
(5) Similar *trans*-furylidene acetates have been prepared: S. J. Danishefsky, *et al.*, private communication.
(6) Since the starting alcohol has a boiling point slightly higher than that of the desired product, partial distillation increased the percentage of lower boiling component in the mixture (**2**, estimated to be better than 85% pure by pmr).

Dissolving Metal Reductions of Benzylic Esters[1a]

J. Hodge Markgraf,* W. Michael Hensley, and Larry I. Shoer[1b]

Department of Chemistry, Williams College, Williamstown, Massachusetts 01267

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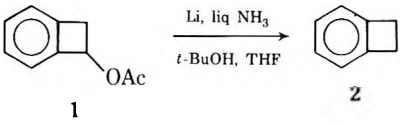
Recently we reported a convenient route to benzocyclobutene (**2**) in which the novel step was the dissolving metal reduction of benzocyclobutenyl acetate (**1**).[2] Although this



1 **2**

reductive cleavage was patterned after a similar reaction of allylic acetates,[3] the above reaction was to our knowledge its first application to a benzylic system. The benzyl moiety is frequently employed as a protecting or activating group because its subsequent removal can be effected by hydrogenolysis[4] or hydrostannolysis.[5] The latter procedure, however, failed to bring about the conversion of **1** to **2**.[2] In view of such a difference, it seemed desirable to define the scope of this dissolving metal reductive cleavage. In order to investigate the effect of the ester group six benzylic compounds were selected: acetate (**3**), benzoate (**4**), carbamate (**5**), formate (**6**), trifluoroacetate (**7**), and thioacetate (**8**). The choice was based on availability, ease of preparation for new applications, and possible biochemical utility.[6]

Two standardized procedures were developed. Method A involved the addition of a solution of the ester and *tert*-butyl alcohol in tetrahydrofuran (THF) to a solution of lithium in liquid ammonia. Method B involved the addition of lithium to a solution of the ester and *tert*-butyl alcohol in liquid ammonia–THF until the color of the reaction solution persisted blue. In both cases, after a standard work-up, the yield of toluene was determined by quantitative gas–liquid chromatography (glc). Since the conditions used (Li, NH_3, *t*-BuOH) can also reduce aromatic rings, it was necessary to consider product contamination by dihydro and tetrahydro derivatives of toluene. The absence of further reduced products was established by two procedures. A mixture of authentic samples of toluene, 1-methyl-1,4-cyclohexadiene, and 1-methylcyclohexene was cleanly resolved by glc analysis, and peaks corresponding to the latter two compounds were absent in the reaction mixture. Also, the hydrocarbon product from the reduction of benzyl acetate by method A was isolated by preparative glc; its nmr spectrum confirmed the presence of toluene exclusively.

The results are summarized in Table I. Method A was developed using a 20% excess of lithium based on the stoichiometry of 2 equiv of lithium per equivalent of ester. Under these conditions only the reductions of **3**, **5**, and **6** proceeded with preservation of the blue color throughout

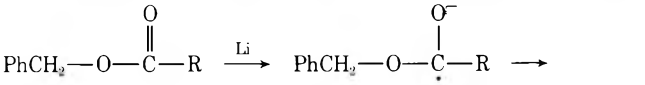
Table I
Reduction of Benzylic Esters (YCH_2Ph) by Lithium in Liquid Ammonia

Compd	Y	Toluene, %[a] Method A[b]	Method B	Li[c]
3	CH_3CO_2-	72	77	25
4	$C_6H_5CO_2-$	30	45	43
5	H_2NCO_2-	77	74	24
6	HCO_2-	67	66	28
7	CF_3CO_2-	51	57	29
8	CH_3COS-	26	83	43

[a] Average value (±2%) of duplicate runs. [b] Ester (10 mmol) added to lithium (24 mg-atoms). [c] Milligram-atoms of lithium added to ester (10 mmol) in order to generate blue reaction solution in method B.

the addition of ester. After attempts to dissolve sufficient lithium for **4**, **7**, and **8** proved unpredictable, method B was employed. This inverse addition procedure proved to be the method of choice for the ease by which appropriate amounts of lithium could be regulated. A further advantage of method B was evident in the smooth and controllable reduction of **5**; this same reaction by method A was exceedingly vigorous. The tabulated data show that method B was equal or superior to method A in all cases studied.

Since no mechanistic studies have been reported for the dissolving metal reductions of allylic or benzylic esters, a few exploratory reactions were included in the present work. Three pathways for the reductive cleavage are possible. The first two routes proceed *via* anion radical **9**, which



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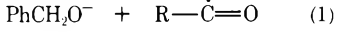

(1)

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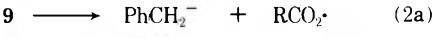

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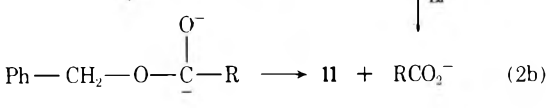

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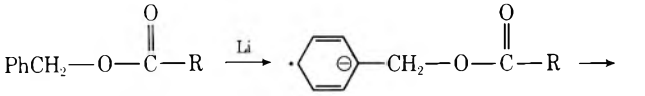

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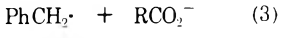

(3)

13

can cleave to generate either alkoxide ion **10** (eq 1), the initial phase of the acyloin condensation,[7] or carbanion **11** (eq 2a), the route postulated by Henbest, *et al.*,[3] for allylic acetates. The dianion in eq 2b represents an alternate precursor of **11**. Initial reduction of the aromatic ring (eq 3) can generate an anion radical suitable for fragmentation to radical **13** which, in turn, would be rapidly reduced to **11**. The chief distinction among these routes centers on whether the key intermediate is an alkoxide ion (**10**) or a carbanion (**11**). In the presence of a proton donor (*t*-BuOH) the generation of **10** would lead to benzyl alcohol (**14**), which can be reduced to toluene.[7] In a separate experiment under the conditions of method A **14** as reactant was converted to toluene in 89% yield. An attempt was made to differentiate between eq 1 and eq 2 or 3 by omitting the *tert*-butyl alcohol and quenching with sodium benzoate or ammonium chloride.[8] The use of sodium benzoate was designed to quench excess lithium and to preserve a benzylic alkoxide in the absence of an external proton source.[9] When applied to **3** this procedure afforded both toluene (14%) and **14** (8%) in low yield. A similar reduction (without added *t*-BuOH) of **3** when quenched with ammonium chloride also produced toluene (30%) and **14** (5%). These results are ambiguous and do not permit a single pathway to be deduced. The production of toluene in the absence of *tert*-butyl alcohol, regardless of the quenching reagent, is consistent with a carbanion intermediate. Alternatively, **10** could be protonated and the resulting **14** reduced to toluene before all of the excess lithium was quenched.[9] Finally, the low yields of toluene in the absence of added *tert*-butyl alcohol support initial ring reduction. It is possible, of course, that not all six esters follow the same pathway. Since the present work was carried out to establish the utility of dissolving metal reductions for the reductive cleavage of benzylic esters, no further studies are planned on the mechanistic aspects.

Experimental Section

Boiling points are uncorrected. Nmr spectra were recorded on a Perkin-Elmer R12B spectrometer, with CCl_4 as solvent and tetramethylsilane as internal standard. Preparative glc separations were performed on an Aerograph A-90-P instrument, fitted with a 0.375 in. × 20 ft column of 20% DC-710 on Chromosorb G.

Materials. Lithium wire (Alfa, 99.9%, 3.2 mm diameter) was stored under anhydrous benzene. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride; a middle fraction was collected and stored under a nitrogen atmosphere. Commercial samples of **3**, **4**, and **6** were distilled *in vacuo* and middle fractions were collected; **5** was used as received. Esters **7** and **8** were prepared by published procedures: **7**[10] (81%), bp 72.3–73.0° (11 mm) [lit.[11] bp 50–52° (5 mm)]; **8**[12] (51%), bp 110–112° (8 mm) [lit.[13] bp 109° (5 mm)]. Samples of 1-methyl-1,4-cyclohexadiene and 1-methylcyclohexene (both 99%) were obtained from Chemical Samples Co.

Dissolving Metal Reduction. Method A. A 50-ml three-neck flask fitted with a Dry Ice–acetone condenser, mechanical stirrer, and gas inlet tube was flushed with argon and immersed in a Dry Ice–acetone bath. Gaseous ammonia was passed through a tower of potassium hydroxide pellets and *ca.* 20 ml was condensed in the flask. To a stirred solution of lithium (0.165 g, 24 mmol, washed and cut under anhydrous diethyl ether) in liquid ammonia was added dropwise from an argon-swept addition funnel a solution of the ester (10 mmol) and *tert*-butyl alcohol (0.74 g, 10 mmol) in THF (5 ml). After the addition was complete (*ca.* 10 min) the dark blue reaction solution was stirred for an additional 30 min, the excess lithium was quenched with solid ammonium chloride, the Dry Ice–acetone bath was removed, and the reaction mixture was allowed to warm to room temperature. After evaporation of the ammonia the flask was chilled in an ice bath, water (5 ml) was added, and the mixture was transferred to a separatory funnel and extracted twice with 7-ml portions of chloroform. The combined extract was washed once with 2 *N* hydrochloric acid and twice with saturated sodium chloride solution, dried over sodium sulfate, filtered into a 25-ml volumetric flask, and diluted to the mark with chloroform. This solution was analyzed by glc.

Method B. A 50-ml three-neck flask fitted as above was flushed with argon and immersed in a Dry Ice–acetone bath. To liquid ammonia (*ca.* 20 ml, condensed as above) was added a solution of the ester (10 mmol) and *tert*-butyl alcohol (0.74 g, 10 mmol) in THF (5 ml). To the stirred reaction solution was added lithium (*ca.* 4-mm lengths of wire washed and cut under diethyl ether) from an argon-swept 10-ml erlenmeyer flask connected to a side arm of the flask by Gooch tubing. Excess lithium was initially placed in the erlenmeyer flask and the actual amount used was determined by difference after sufficient lithium was added slowly (*ca.* 90 min) to generate a persistent dark blue solution. The color was discharged by

the addition of solid ammonium chloride, and the subsequent work-up procedure was the same as above.

Glc Analysis. Analysis of the chloroform solutions of toluene (prepared in 25-ml volumetric flasks) was conducted on a Varian 1420 instrument with a 0.125 in. × 10 ft column of 10% Dow Corning 710 on Chromosorb W, helium flow rate of 30 ml/min, and column temperature of 100°. The following retention times (in minutes) were observed: 1-methylcyclohexene, 3.7; toluene, 4.6; 1-methyl-1,4-cyclohexadiene, 5.2; benzyl alcohol, 37. Each product solution was analyzed in triplicate using a fixed-volume injection and the average peak height was related to millimoles of toluene by a least-squares computer plot of peak heights *vs.* known concentrations of toluene. The precision of this method was ±1%. Each reduction was carried out at least twice and the data in Table I are average values (±2%).

A control experiment in which a solution of toluene (10 mmol) and *tert*-butyl alcohol (10 mmol) in THF was added to a solution of lithium (3 mg-atoms) in liquid ammonia and the reaction solution was subjected to the standard work-up and glc analysis established that 90% of the toluene was recovered.

Acknowledgment. This work was supported in part by funds from a grant to Williams College from the Alfred P. Sloan Foundation.

Registry No.—**3**, 140-11-4; **4**, 120-51-4; **5**, 621-84-1; **6**, 104-57-4; **7**, 351-70-2; **8**, 32362-99-5; lithium, 7439-93-2.

References and Notes

(1) (a) Presented at the 5th Northeast Regional Meeting of the American Chemical Society, Rochester, N. Y., Oct 1973; (b) based on the Honors Thesis of L. I. Shoer, Williams College, 1973.
(2) J. H. Markgraf, S. J. Basta, and P. M. Wege, *J. Org. Chem.*, **37**, 2361 (1972).
(3) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).
(4) W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263 (1953).
(5) L. E. Khoo and H. H. Lee, *Tetrahedron Lett.*, 4351 (1968).
(6) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, Wiley, New York, N. Y., 1961, pp 1239–1243.
(7) H. Smith, "Organic Reactions in Liquid Ammonia, Chemistry in Anhydrous Liquid Ammonia," Vol. 1, Wiley, New York, N. Y., 1963, Part 2, pp 160–161, 173–181.
(8) We thank a referee for assistance with the mechanistic interpretations.
(9) (a) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971); (b) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971).
(10) V. T. Oliverio and E. Sawicki, *J. Org. Chem.*, **20**, 363 (1955).
(11) A. C. Pierce and M. M. Joullie, *J. Org. Chem.*, **27**, 3968 (1962).
(12) A. A. Chilingaryan, Y. Y. Usaevich, and A. Y. Nazarov, *Tr. Leningrad. Khim.-Farm. Inst.*, 5 (1962); *Chem. Abstr.*, **60**, 10541*i* (1964).
(13) B. Wladislaw, H. Viertler, and E. B. Demant, *J. Chem. Soc. B*, 565 (1971).

Thiophenyl Malonate. A New Synthesis

G. Edwin Wilson, Jr.,* and Arye Hess

Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn, New York 11201

Soma Kumar

Department of Chemistry, Georgetown University, Washington, D. C. 20057

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We wish to report a convenient procedure for synthesizing thiophenyl malonate, the active ester of choice for forming malonyl coenzyme A, based upon the reaction of malonic acid monochloride with thiophenol. We were led to develop this synthesis when we discovered that scaling up the normal procedure of Trams and Brady,[1,2] which involves coupling malonic acid with thiophenol using dicyclohexylcarbodiimide, produced no thiophenyl malonate but only a bright orange crystalline side product. In addition we had observed that some preparations of malonyl coenzyme A obtained from thiophenyl malonate synthesized by the Trams and Brady procedure were inexplicably one-half to one-third as active as others when used as substrate in enzymatic synthesis of fatty acids, indicative of the possible presence of inhibitory by-products.

The thiol ester obtained in low (13%) yield from the reaction of acid chloride with thiophenol is a colorless, stable solid. Using this material, a 10-mg sample of coenzyme A (approximately 10 μmol) yields about 8 μmol of malonyl coenzyme A.[1] The malonyl coenzyme A produced is fully active in reactions catalyzed by pigeon liver and rabbit mammary fatty acid synthetases as assayed spectrophotometrically in the presence of acetyl coenzyme A and NADPH.

Malonic Acid Monochloride. Malonic acid (15.6 g, 0.15 mol) and thionyl chloride (18 g, 0.15 mol) in 60 ml of ether were heated under reflux for 6 hr with stirring in a flask surmounted with a condenser and drying tube. During the reflux period, evolution of hydrogen chloride was observed. The solvent was then removed on a rotary evaporator under vacuum, and the remaining solid was triturated at 40° with ten 30-ml portions of a 1:2 mixture of chloroform–hexane. The combined extract was cooled to −15° and allowed to crystallize. The yellow crystals (5.27 g, 28.7%) of malonic acid monochloride were washed with hexane and dried overnight under vacuum, mp 58–61° (lit.[3] mp 63–65°).

Thiophenyl Malonate (Shirley's Ester). Thiophenol (1.9 g, 0.017 mol) was added dropwise to a stirred solution of 2.1 g (0.015 mol) of malonic acid monochloride in 25 ml of ether under an atmosphere of dry argon. The reaction was allowed to continue for 3 hr, after which time the solvent was removed on a rotary evaporator, leaving a moist solid which was placed under a vacuum of 0.1 mm until no more yellowish oil (thiophenol) could be observed. The majority of the solid was then dissolved in a minimum amount of chloroform and filtered to provide a clear yellow solution. Addition of hexane to the cloud point and subsequent cooling resulted in crystallization, providing a yellow solid, mp 57–68°. Dissolution in chloroform, decolorization with carbon, addition of hexane, and cooling in a Dry Ice–acetone bath provided 0.37 g (13%) of colorless crystals of thiophenyl malonate, mp 69–71° (lit.[2] mp 72–73°), which were collected and dried under vacuum: nmr ($CDCl_3$) δ 3.70 (s, 2 H), 7.42 (s, 5 H), 10.73 (s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 196 (0.1, M^+), 152 (1.4, $M^+ - CO_2$), 110 (100, $PhSH^+$); ir (KBr) 1690 (O=CS), 1718 cm^{-1} (O=CO).

Anal. Calcd for $C_9H_8O_3S$: C, 55.09; H, 4.11; S, 16.34. Found: C, 54.79; H, 4.30; S, 16.61.

Registry No.—Malonic acid monochloride, 51932-41-3; malonic acid, 141-82-2; thionyl chloride, 7719-09-7; thiophenyl malonate, 4279-77-0; thiophenol, 108-98-5.

References and Notes

(1) E. G. Trams and R. O. Brady, *J. Amer. Chem. Soc.*, **82**, 2972 (1960).
(2) J. C. Howard, M. C. Lin, P. Matthews, and S. A. Singal, *J. Med. Chem.*, **8**, 888 (1965).
(3) H. Eggerer and F. Lynen, *Biochem. Z.*, **335**, 519 (1962).

Catalysis by Certain Amines in an Aqueous Phase. Preparation of Dichlorocyclopropane Derivatives

Kakuzo Isagawa,* Yoshikazu Kimura, and Sundo Kwon

Department of Applied Chemistry, College of Engineering, University of Osaka Prefecture, Sakai, Osaka, 591, Japan

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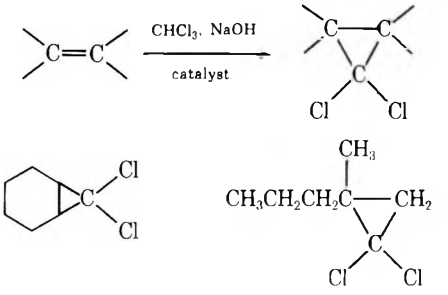
Dihalocarbenes are considered synthetically useful species for cyclopropane ring formation. The preparation of dichlorocyclopropane derivatives with concentrated aqueous sodium hydroxide and chloroform in the presence of quaternary ammonium or phosphonium salts was recently reported.[1-3] On the other hand, it is said that tertiary amines have catalytic effect for some reactions between aqueous and organic layers.[4,5]

We now report the catalytic effect of tertiary amines for the preparation of dichlorocyclopropane derivatives by the reaction of olefins with concentrated aqueous sodium hydroxide and chloroform.

The reaction was carried out using cyclohexene or 2-methyl-1-pentene with tertiary amines as the catalyst to give dichloronorcarane (1) and 1-methyl-1-*n*-propyl-2,2-dichlorocyclopropane (2), respectively. As tertiary amines,



trialkylamines (C_2–C_6, C_8, and C_{10}), *N*-*n*-butylpiperidine, *N*,*N*-diethylaniline, and triethanolamine were used. Primary amines, secondary amines, tertiary amine hydrogen halides, and tetraalkylammonium halides were used, in order to study the catalytic effect of other amines or quaternary ammonium salts. The results of catalytic effects of some amines and ammonium salts in the formation of dichloronorcarane are given in Table I.

We found that trialkylamines, their hydrogen halides, and the corresponding tetraalkylammonium halides showed significant catalytic effects, but the primary and secondary amines did not. Trialkylamines exhibited the same effects as trialkylamine hydrogen halides and tetraalkylammonium halides. For example, tri-*n*-butylamine gave 1 in 75% yield, and in the cases of tri-*n*-butylamine hydrogen chloride and tetra-*n*-butylammonium bromide, the yields of 1 were 77 and 76%, respectively. In addition, trialkylamines having the alkyl groups of C_4 and C_5 showed better effects than other trialkylamines.

The catalytic effects of tertiary amines in the formation of 2 by the addition of a dichlorocarbene to 2-methyl-1-pentene were similar to those observed in the formation of 1. The amines or ammonium salts (yield of 2) follow: *N*-*n*-butylpiperidine (83%), *N*-*n*-butylpiperidine hydrogen bromide (86%), *N*,*N*-di-*n*-butylpiperidinium iodide (86%).

Thus, we found that trialkylamine was able to form a dichlorocarbene from chloroform and to give dichlorocyclopropane derivatives. An experiment using stoichiometric quantities of olefin (44 mmol) and trialkylamine (44 mmol) in chloroform (11 ml, 135 mmol) without aqueous sodium hydroxide at 50° for 2 hr failed to form dichlorocyclopropane derivatives. Therefore, it seems likely that trialkylamine does not react directly with chloroform; the sodium hydroxide appears to be essential for the formation of dichlorocarbene.

It is very interesting that trialkylamine is effective in this phase transfer catalysis reaction.

Experimental Section

Melting points are uncorrected. Mass spectra were run on a Hitachi RMU-6E mass spectrometer. Infrared spectra were recorded on a Hitachi Model 215 infrared spectrophotometer. Gas chromatographic analyses were performed on a Hitachi Model 063 gas chromatograph using a 3 mm × 1 m column of Silicone SE-30 on

Table I
Catalytic Effects of Amines and Quaternary Ammonium Salts in the Formation of Dichloronorcarane

Amine or quaternary ammonium salt	Yield of dichloronorcarane, %	Amine or quaternary ammonium salt	Yield of dichloronorcarane, %
None	<1	Tri-*n*-decylamine	45
Triethylamine	33	*n*-Laurylamine	<1
Triethylamine hydrogen chloride	35	Piperidine	<1
		N-*n*-Butylpiperidine	73
Tetraethylammonium chloride	31	*N*-*n*-Butylpiperidine hydrogen bromide	76
Tri-*n*-propylamine	67	*N*,*N*-Di-*n*-butylpiperidinium iodide	75
n-Butylamine	<1		
tert-Butylamine	4	Piperazine	<1
Di-*n*-butylamine	<1	Pyridine	<1
Tri-*n*-butylamine	75	*N*-*n*-Butylpyridinium bromide	<1
Tri-*n*-butylamine hydrogen chloride	77		
		N-*n*-Hexadecylpyridinium bromide	<1
Tetra-*n*-butylammonium bromide	76		
		Aniline	<1
Tri-*n*-amylamine	73	*N*-Ethylaniline	<1
Triisoamylamine	79	*N*,*N*-Diethylaniline	<1
Tri-*n*-hexylamine	65	Triethanolamine	<1
Tri-*n*-octylamine	65		

Chromosorb W AW (80–100 mesh). Elemental analyses were done on a Hitachi Model 026 CHN analyzer.

Reagents. Cyclohexene, 2-methyl-1-pentene, amines, and quaternary ammonium salts, except for some compounds described below, were commercial reagents and purified by distillation or recrystallization. Chloroform was commercial reagent and distilled twice.

Tri-*n*-butylamine hydrogen chloride was prepared by treatment of tri-*n*-butylamine with dry hydrogen chloride.[6]

***N*-*n*-Butylpyridinium bromide** was prepared from pyridine and *n*-butyl bromide by the method reported earlier.[7]

***N*-*n*-Butylpiperidine** was prepared from piperidine and *n*-butyl bromide by the method reported earlier.[8]

***N*-*n*-Butylpiperidine Hydrogen Bromide.** A solution of 2.4 g (25 mmol) of piperidine and 3.4 g (25 mmol) of *n*-butyl bromide in 20 ml of ethanol was refluxed for 2 hr. The reaction mixture was cooled and ethanol was removed. Dry ether was added to the residue and the mixture was stirred. A white solid was precipitated. The solid was washed with dry ether several times. It was recrystallized from absolute ethanol–ether (9:1) as white needles, mp 220–222°.

Anal. Calcd for $C_9H_{20}NBr$: C, 48.66; H, 9.07; N, 6.30. Found: C, 48.88; H, 9.41; N, 6.37.

***N,N*-Di-*n*-butylpiperidinium Iodide.** A solution of 2.4 g (25 mmol) of piperidine and 9.2 g (50 mmol) of *n*-butyl iodide in 20 ml of ethanol was refluxed for 0.5 hr. The reaction mixture was cooled and ethanol was removed. Dry ether was added to the residue and the mixture was stirred. A light yellow solid was precipitated. The solid obtained was collected by filtration and washed several times with dry ether. It was recrystallized from absolute ethanol–*n*-hexane (9:1) as light yellow needles, mp 222–223°.

Anal. Calcd for $C_{13}H_{28}NI$: C, 48.00; H, 8.68; N, 4.31. Found: C, 48.37; H, 8.87; N, 3.90.

Preparation of Dichlorocyclopropane Derivatives. A mixture of olefin (44 mmol), chloroform (11 ml, 135 mmol), and amine or quaternary ammonium salt (0.44 mmol) was stirred at 50°. An aqueous solution prepared from 13.5 g of sodium hydroxide and 27 ml of water was added during 15 min. After 2 hr of stirring the mixture was acidified with 10% sulfuric acid and extracted five times with 30-ml portions of ether. The combined ether extract was dried over calcium chloride, allowed to stand overnight, and evaporated to an oily liquid. The liquid was distilled and identified by mass spectrography. The yield of the product was determined by gas chromatography.

Dichloronorcarane (1). This compound was obtained from cyclohexene: bp 79–81° (15 mm) [lit.[9] bp 79–80° (15 mm)]; mass spectrum *m/e* 164 (P), 166 (P + 2); the P:(P + 2) ratio of relative intensity was *ca.* 3:2 (2 Cl). This material had an infrared spectrum identical with that of authentic dichloronorcarane.[10]

1-Methyl-1-*n*-propyl-2,2-dichlorocyclopropane (2). This compound was obtained from 2-methyl-1-pentene: bp 163–165°; mass spectrum *m/e* 166 (P), 168 (P + 2); the P:(P + 2) ratio of relative intensity was *ca.* 3:2 (2 Cl).

Acknowledgment. We thank Dr. S. Nakanishi for helping to obtain the mass spectra.

Registry No.—**1,** 823-69-8; **2,** 52259-98-0; chloroform, 67-66-3; cyclohexene, 110-83-8; 2-methyl-1-pentene, 763-29-1; tri-*n*-propylamine, 102-69-2; tri-*n*-butylamine, 102-82-9; tri-*n*-butylamine hydrogen chloride, 6309-30-4; tetra-*n*-butylammonium bromide, 1643-19-2; tri-*n*-amylamine, 621-77-2; triisoamylamine, 645-41-0; tri-*n*-hexylamine, 102-86-3; tri-*n*-octylamine, 1116-76-3; *N*-*n*-butylpiperidine, 4945-48-6; *N*-*n*-butylpiperidine hydrogen bromide, 51359-83-2; *N,N*-di-*n*-butylpiperidinium iodide, 52259-97-9.

References and Notes

(1) M. Makosza and M. Wawrzyniewicz, *Tetrahedron Lett.*, 4659 (1969).
(2) G. C. Joshi, N. Singh, and L. M. Pande, *Tetrahedron Lett.*, 1461 (1972).
(3) C. M. Starks, *J. Amer. Chem. Soc.*, **93,** 195 (1971).
(4) M. J. Jarrousse, *C. R. Acad. Sci., Ser. C,* **232,** 1424 (1951).
(5) Y. Yamamoto and T. Shimamura, *Kogyo Kagaku Zasshi,* **60,** 423 (1957).
(6) V. Deitz and R. M. Fuoss, *J. Amer. Chem. Soc.*, **60,** 2394 (1938). The pure sample was not obtained, because recrystallization of this compund was very difficult. In the earlier report, the purification of the compound was unsuccessful.
(7) M. Katcka and T. Urbanski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **12,** 615 (1964); *Chem. Abstr.*, **62,** 11662 (1965).
(8) H. W. Magnusson and E. R. Shierz, *Univ. Wyo., Publ.*, **7,** 1 (1940); *Chem. Abstr.*, **34,** 6867 (1940).
(9) W. I. Bevan, R. N. Haszelcline, and J. C. Young, *Chem. Ind. (London)*, 789 (1961).
(10) W. von E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **76,** 6162 (1954).

Arylation of Arenethiolate Ions by the $S_{RN}1$ Mechanism. A Convenient Synthesis of Diaryl Sulfides.

Summary: Aryl iodides react with arenethiolate ions in liquid ammonia under irradiation by Pyrex-filtered light to form diaryl sulfides in good yields, probably by the $S_{RN}1$ mechanism.

Sir: The recently recognized $S_{RN}1$ mechanism of aromatic substitution[1] involves radical and radical anion intermediates and electron-transfer steps. Heretofore it has been observed with nitranion (NH_2^-, $PhNH^-$)[1,2b] and several kinds of carbanion nucleophiles.[2a,c-e,3] Arenethiolate ion nucleophiles are, however, known to participate in $S_{RN}1$ reactions at saturated carbon sites[4] and in the 4 position of the isoquinoline system.[5] We now report conditions in which arenethiolate ions react very satisfactorily at benzene ring sites, probably by the $S_{RN}1$ mechanism.

When solutions of an aryl iodide and an arenethiolate ion in refluxing liquid ammonia (−33°) under nitrogen are irradiated with Pyrex-filtered light, reaction occurs to form a diaryl sulfide, according to Chart I. The arenethiolate ion can be supplied with sodium or potassium gegenion or, more conveniently, by dissolving the arenethiol in ammonia with which it undergoes an acid–base reaction. Several reactions of this type are summarized in Table I.

Chart I

$$ArI + Ar'S^- \xrightarrow[NH_3]{h\nu} ArSAr' + I^-$$

Preparatively, this procedure is attractive for preparation of diaryl sulfides on about a 10-g scale. The procedure is simple and conditions are mild. The aryl iodide is simply mixed with thiophenol and ammonia is condensed. Photostimulation in a 350-nm photochemical reactor leads to a facile substitution reaction. Despite the low solubility of certain aryl iodides in liquid ammonia, reaction still occurs. Upon completion of the reaction, the ammonia is allowed to evaporate. An aqueous work-up followed by simple distillation or recrystallization affords the diaryl sulfide in high purity. Other methods for the preparation of diaryl sulfides mostly involve long periods of heating at temperatures of 175° or higher, or explosive intermediates, or other unwelcome features.[6]

Aryl bromides also react, but much more slowly than aryl iodides.

The presumed mechanism is sketched in Chart II. This is the standard $S_{RN}1$ mechanism[1] adapted to the immediate case. Photons probably stimulate electron transfer from thiolate ion to aryl iodide (eq 1), and thus are involved in initiation of a chain mechanism.

Chart II

$$Ar'S^- + ArI \xrightarrow{h\nu} Ar'S\cdot + [ArI]\cdot^- \quad (1)$$

$$[ArI]\cdot^- \longrightarrow Ar\cdot + I^- \quad (2)$$

$$Ar\cdot + Ar'S^- \longrightarrow [ArSAr']\cdot^- \quad (3)$$

$$[ArSAr']\cdot^- + ArI \longrightarrow ArSAr' + [ArI]\cdot^- \quad (4)$$

$$\text{termination steps} \quad (5)$$

The low yield of sulfide from 2-iodo-*m*-xylene is due in part to a substantial fraction of the 2,6-dimethylphenyl radicals being diverted to *m*-xylene. Combination of thiophenoxide ion with that radical is apparently hindered significantly by the ortho methyl groups. In contrast, a pair of

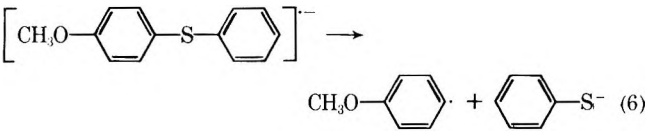
Table I
Photoinitiated Reaction of Aryl Iodides with Thiophenoxide in Liquid Ammonia

Run no.	Substrate	Reaction time, min	Sulfide product	% yield[a]	Other products[b]
1	PhI	70	PhSPh	94[c]	
2	1-Iodonaphthalene	75	1-$PhSC_{10}H_7$	85[d]	Naphthalene
3	*o*-$CH_3OC_6H_4I$	90	*o*-$MeOC_6H_4SPh$	91[d]	Anisole
4	*m*-$MeOC_6H_4I$	90	*m*-$MeOC_6H_4SPh$	88[d]	Anisole
5	*p*-$MeOC_6H_4I$	30	*p*-$MeOC_6H_4SPh$	76[e]	Anisole
6	*o*-$CH_3C_6H_4I$	165	*o*-$CH_3C_6H_4SPh$	68[f]	Toluene, PhSSPh
7	*m*-$CH_3C_6H_4I$	135	*m*-$CH_3C_6H_4SPh$	81[e]	Toluene
8	*p*-$CH_3C_6H_4I$	360	*p*-$CH_3C_6H_4SPh$	72[g]	Toluene, PhSSPh
9	2-iodo-*m*-xylene	140	2-PhS-*m*-xylene	19[c,h]	*m*-xylene (28%)[c] PhSSPh (36%)[i]
10	*m*-FC_6H_4I	100	*m*-FC_6H_4SPh	96	
11	*p*-IC_6H_4OPh	120	*p*-$PhSC_6H_4OPh$	92	PhOPh, PhSPh
12	*m*-$IC_6H_4CF_3$	170	*m*-$PhSC_6H_4CF_3$	71[d]	*m*-$PhSC_6H_4CF_2SPh$ (16%)
13	PhBr	120	PhSPh	23[j]	
14	$C_5H_5FeC_5H_4I$	60			$C_5H_5FeC_5H_5$ (15%)[c] PhSSPh (17%)[c]

[a] Isolated yield unless otherwise indicated. [b] Trace amounts unless otherwise indicated. [c] Yield by gc. [d] Trace of unreacted starting material remaining. [e] Approximately 10% unreacted aryl iodide remaining. [f] 18% unreacted o-iodotoluene. [g] 14% unreacted *p*-iodotoluene. [h] 39% unreacted 2-iodo-*m*-xylene.[c] [i] Yield based on 2-iodo-*m*-xylene. [j] Based on bromide titration; mostly unreacted bromobenzene recovered.

ortho methyl groups does not appear to affect combination of an aryl radical with the amide ion[2b] or with picolyl anions.[3b] Formation of *m*-xylene from its 2-iodo derivative represents reduction; the concomitant product of oxidation is diphenyl disulfide.

A companion experiment to run 5, Table I, was reaction of iodobenzene with *p*-methoxybenzenethiolate ion (120 min) to form phenyl *p*-methoxyphenyl sulfide in 71% yield. It is significant that no trace of bis(*p*-methoxyphenyl) sulfide was found as a product. Alkali metal cleavage of phenyl *p*-methoxyphenyl sulfide in ammonia or methylamine affords thiophenol and anisole,[7] indicating that its radical anion undergoes fission as shown in eq 6.[2e] If *p*-methoxyphenyl radical were formed in the presence of *p*-methoxybenzenethiolate ion, some bis(*p*-methoxyphenyl) sulfide should be formed. We conclude that in this system the phenyl *p*-methoxyphenyl sulfide radical anion transfers an electron to iodobenzene (eq 4) faster than it splits as in eq 6.



(6)

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References and Notes

(1) J. K. Kim and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 7463, 7464 (1970).
(2) R. A. Rossi and J. F. Bunnett: (a) *J. Amer. Chem. Soc.*, **94**, 683 (1972); (b) *J. Org. Chem.*, **37**, 3570 (1972); (c) *ibid.*, **38**, 1407 (1973); (d) *ibid.*, **38**, 3020 (1973); (e) *J. Amer. Chem. Soc.*, **96**, 112 (1974).
(3) J. F. Bunnett and B. F. Gloor: (a) *J. Org. Chem.*, **38**, 4156 (1973); (b) *ibid.*, **39**, 382 (1974).
(4) N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Amer. Chem. Soc.*, **89**, 725 (1967).
(5) J. A. Zoltewicz and T. M. Oestreich, *J. Amer. Chem. Soc.*, **95**, 6863 (1973).
(6) A. Schöberl and A. Wagner, in E. Müller, "Methoden der Organischen Chemie (Houben-Weyl)," Vol. IX 1955, p 93. J. H. Uhlenbroek, *Recl. Trav. Chim. Pays-Bas*, **80**, 1057 (1961). J. R. Campbell, *J. Org. Chem.*, **27**, 2207 (1962); **29**, 1831 (1964).
(7) W. E. Truce, D. P. Tate, and D. N. Burdge, *J. Amer. Chem. Soc.*, **82**, 2872 (1960).

University of California
Santa Cruz, California 95064
J. F. Bunnett*
Xavier Creary

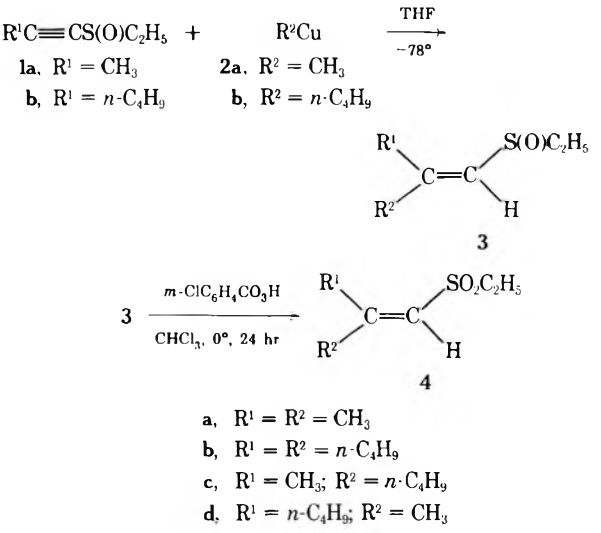
Received July 8, 1974

The Addition of Organocopper(I) Reagents to α,β-Acetylenic Sulfoxides[1,2]

Summary: Monoalkylcopper(I) reagents (**2**) add to α,β-acetylenic sulfoxides (**1**) with almost exclusive cis stereoselectivity to form β-alkylated α,β-ethylenic sulfoxides (**3**) in high yield.

Sir: Organocopper(I) reagents add to a variety of α,β-unsaturated compounds,[3] including α,β-ethylenic sulfones[4] and α,β-acetylenic esters[5] and acids.[5c,6] Our continuing interest in nucleophilic additions to activated acetylenes,[7] and in the ability of organosulfur functionalities to activate the triple bond toward conjugate addition, prompted an investigation of the reaction of organocopper(I) reagents with α,β-acetylenic sulfur compounds.

We have found that α,β-acetylenic sulfoxides (**1**)[8] react readily with monoalkylcopper(I) reagents (**2**) to produce, after work-up, high yields of the corresponding β-alkylated α,β-ethylenic sulfoxides (**3**). Furthermore, the addition reaction was shown to be highly stereoselective, producing the product of cis addition to the triple bond almost exclusively.



(1)

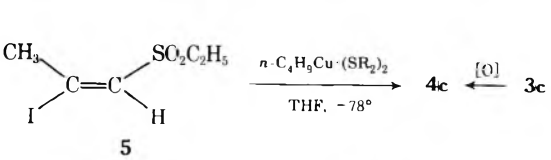
(2)

a, $R^1 = R^2 = CH_3$
b, $R^1 = R^2 = n\text{-}C_4H_9$
c, $R^1 = CH_3$; $R^2 = n\text{-}C_4H_9$
d, $R^1 = n\text{-}C_4H_9$; $R^2 = CH_3$

The following procedures are representative. Into a 50-ml flask, equipped with a stopple-covered side arm, an adapter tube with stopcock connected to a mercury bubbler, and a magnetic stirring bar, is weighed 0.727 g (3.82 mmol, 2% in excess of the alkyllithium reagent to be used) of cuprous iodide. After oven drying, the flask is cooled while flushing with nitrogen, 12.9 ml of dry THF is injected, and to the resulting suspension at 0° is added 2.1 ml (3.74 mmol) of a 1.78 *M* solution of methyllithium in diethyl ether over a 2-min period. The resulting suspension of methylcopper(I) (25% excess) is cooled to −78° for 15 min and a solution of 0.473 g (2.99 mmol) of ethyl 1-hexynyl sulfoxide (**1b**) in 12.0 ml (~0.25 *M*) of dry THF, precooled to −78°, is injected rapidly. After stirring for 1.5 hr at −78° the reaction mixture is quenched by injecting 5 ml of methanol precooled to −78° and then pouring into 25 ml of saturated aqueous ammonium chloride solution. Extraction with dichloromethane (3 × 25 ml), drying over $MgSO_4$, and evaporation *in vacuo* gives 0.549 g (>100%) of **3d**. In a similar manner the reaction of 3.87 mmol (25% excess) of *n*-butylcopper(I) in THF (~0.25 *M*) with 0.360 g (3.1 mmol) of ethyl 1-propynyl sulfoxide (**1a**) in 12.4 ml of dry THF for 2 hr at −78° followed by quenching with precooled methanol and work-up gives 0.531 g (98%) of the other geometrical isomer, **3c**.

It was also shown that the α,β-ethylenic sulfoxides **3** can be oxidized almost quantitatively to the corresponding sulfones **4** (with no evidence of isomerization about the double bond) by treatment with 1 equiv of *m*-chloroperbenzoic acid in chloroform at 0° for 24 hr.[10]

The cis stereoselectivity of the organocopper(I) addition to α,β-acetylenic sulfoxides was established unambiguously[11] by an alternate stereospecific synthesis of sulfone **4c**. The reaction of the iodovinyl sulfone **5** with 2.5 equiv of *n*-butylcopper–bis(diisopropyl sulfide) complex[12,13] in dry



(3)

(4)

THF at −78° for 5 hr gives an 88% yield of **4c** with 97.5% stereospecificity. Compound **5** is in turn obtained *via* the known stereoselective addition of a sulfonyl iodide to an acetylene,[14] in 56% isolated yield.

It is interesting to note that, while monoalkylcopper(I) reagents add cleanly to α,β-acetylenic sulfoxides, lithium dialkylcuprates may also give a product resulting from the cleavage of the acetylenic sulfoxide. While lithium dimethylcuprate adds normally to **1a** (83%) and **1b** (97.5%, >96% cis addition), the more reactive lithium di-*n*-butylcuprate reacts to give appreciable quantities of *n*-butyl ethyl sulfoxide (**6**) as well, apparently arising from attack by the organocopper(I) reagent at sulfur rather than on the triple bond.

$$1 + (n\text{-}C_4H_9)_2CuLi \xrightarrow[-78°]{THF} \underset{\mathbf{6}}{n\text{-}C_4H_9S(O)C_2H_5} + 3 \qquad (5)$$

Like results have been observed for additions of organocopper(I) reagents to α,β-acetylenic sulfones,[8] ethyl 1-propynyl sulfone giving an 81% yield of adduct with lithium di-*n*-butylcuprate and a 90% yield with *n*-butylcopper. However, here a difference between the two types of organocopper(I) reagents is manifest in the stereochemistry of the product, *n*-butylcopper giving 92% cis addition while di-*n*-butylcuprate gives, on work-up, 81% of the product, which would correspond to overall trans addition.[15]

References and Notes

(1) Presented at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., March 31–April 5, 1974, Abstract ORGN-70.
(2) Financial support for this work was provided in part by the National Institutes of Health, Grant CA-04536, for which the authors are grateful.
(3) For a recent review, see G. H. Posner, *Org. React.*, **19**, 1 (1972).
(4) G. H. Posner and D. J. Brunelle, *J. Org. Chem.*, **38**, 2747 (1973).
(5) (a) E. J. Corey and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 1851 (1969); (b) J. B. Siddall, M. Biskup, and J. H. Fried, *ibid.*, **91**, 1853 (1969); (c) J. Klein and R. M. Turkel, *ibid.*, **91**, 6186 (1969).
(6) (a) Very recently, the addition of organocopper(I) reagents, generated from Grignard reagents, to α,β-acetylenic sulfides has been reported: P. Vermeer, C. de Graff, and J. Meijer, *Recl. Trav. Chim. Pays-Bas*, **93**, 24 (1974). (b) A study of the reaction of organocopper(I) reagents with α,β-acetylenic sulfoxides has also been undertaken: J. Meijer, private communication.
(7) W. E. Truce and G. J. W. Tichenor, *J. Org. Chem.*, **37**, 2391 (1972).
(8) Prepared from the corresponding α,β-acetylenic sulfides[9] by oxidation with 1.0 equiv of *m*-chloroperbenzoic acid in chloroform at 0° for 24 hr, whereas reaction of the sulfide with 2.0 equiv of the peracid under the same conditions produces the corresponding α,β-acetylenic sulfones: W. E. Truce and L. D. Markley, *J. Org. Chem.*, **35**, 3275 (1970).
(9) For the preparation of α,β-acetylenic sulfides, see J. F. Arens, *Advan. Org. Chem.*, **2**, 117 (1960), and references cited therein.
(10) Glpc analysis of the product of **1a** and **2b**, after oxidation to the sulfone, on an Aerograph Autoprep A-700 chromatograph using an 8 ft × 0.25 in. 15% neopentyl glycol isophthalate on 60–80 mesh Chromosorb W column at 190° and 45 ml/min shows 98.8% cis addition. Similarly, **1b** and **2a** give >96% cis addition. The direct glpc analysis of the sulfoxide products from these reactions, however, proves to be difficult owing to thermal decomposition at the temperatures necessary to elute them from even nonpolar (SE-30, SF-96) columns.
(11) The stereochemistry of the sulfoxide products and their corresponding sulfones is also indicated by their ^{1}H nmr spectra [in $CDCl_3$, parts per million (δ) downfield from tetramethylsilane]. The allylic methyl group in **3c** appears further downfield (1.97; sulfone **4c**, 2.14) than in **3d** (1.92; sulfone **4d**, 1.95) and the allylic methylene group in **3c** appears further upfield (2.20; sulfone **4c** 2.22) than in **3d** (2.42; sulfone **4d**, 2.61).
(12) (a) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967). (b) E. J. Corey and G. H. Posner, *ibid.*, **90**, 5616 (1968). (c) We have found that a similar reaction of lithium di-*n*-butylcuprate with **5** in THF at −78° is *not* stereospecific, giving an 80:20 mixture of **4c** and **4d**.
(13) E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, 1611 (1973).
(14) W. E. Truce and G. C. Wolf, *J. Org. Chem.*, **36**, 1727 (1971).
(15) J. R. Allison, unpublished results, this laboratory.
(16) Texaco Fellow in Organic Chemistry, 1973–1974.

Department of Chemistry
Purdue University
West Lafayette, Indiana 47907

William E. Truce*
Michael J. Lusch[16]

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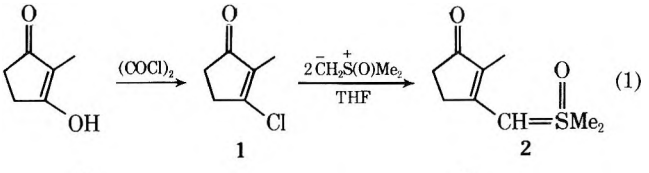
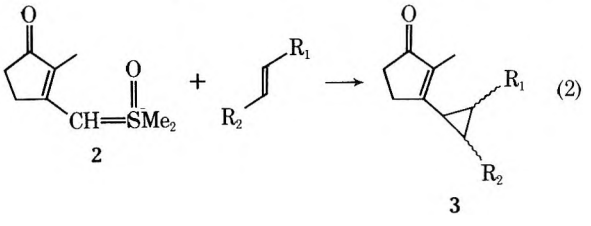
A New and Efficient Approach to Functionalized Hydroazulenes *via* 2-Methylcyclopentenone 3-Dimethylsulfoxonium Methylide[1]

Summary: A three-step sequence for the construction of functionalized hydroazulenes **5** is described starting from the novel cyclopentenone ylide **2.** The preparation of **2,** its reactions with Michael acceptors to produce vinyl cyclopropanes such as **3,** and the use of the divinylcyclopropane rearrangement to generate the bicyclo[5.3.0]decadienone system are described.

Sir: Recently, many sesquiterpenes possessing a hydroazulene skeleton have been isolated,[2] some of which have exhibited significant medicinal properties.[3] Despite the many efforts in the area of hydroazulene synthesis,[4] there are a very limited number of approaches which could accommodate a multitude of sensitive oxygen functionality. Our interest in sesquiterpene lactones possessing the guaiane and pseudoguaiane skeletons has resulted in the development of the synthetic scheme described in this communication. We have recently reported on the reactions and synthetic applications of carbonyl stabilized allyl sulfoxonium ylides.[5] In this communication we wish to report on the preparation of 2-methylcyclopentenone 3-dimethylsulfoxonium methylide (**2**), its reactions with several Michael acceptors, and its utility in the synthesis of functionalized hydroazulenes.

Sulfoxonium ylide **2** was prepared in at least 50% overall yield from the commercially available 2-methyl-1,3-cyclopentanedione. The 1,3-dione was treated with excess oxalyl chloride to produce the 3-chloro-2-methyl-2-cyclopentenone (**1**).[6] Treatment of the vinyl chloride **1** with 2 equiv of dimethylsulfoxonium methylide in tetrahydrofuran resulted in the formation of the crystalline ylide **2** (mp 170–173°).[7,8]





This new allyl ylide reacted cleanly with Michael acceptors such as acrolein, crotonaldehyde, and methyl vinyl ketone to produce vinyl cyclopropanes **3a–c** (see Table I).[5a]

Table I

	R_1	R_2	React temp, °C	React time, hr	Yield, %
3a	CHO	H	R.T.	3	70
3b	CHO	CH_3	56	8	50
3c	$COCH_3$	H	56	4	75

Usually the reaction was carried out using 1.5 to 2.0 equiv of the Michael acceptor in acetonitrile. Cyclopropanes **3a–c** were isolated in a very pure state by evaporation of the acetonitrile and washing the ethyl acetate solution of the residue with water. Cyclopropane **3a** consisted of a 7:1 mixture

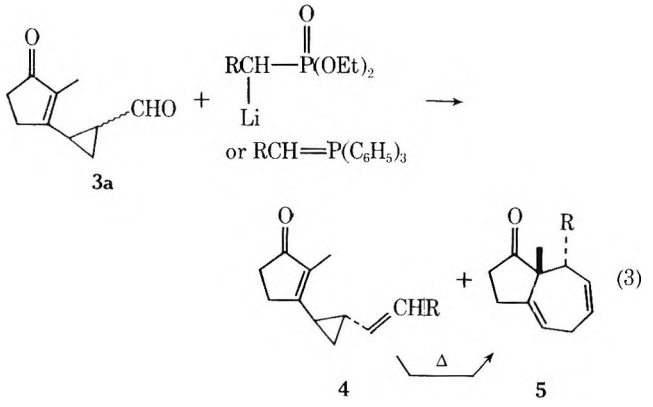
Table II

	R[a]	Yield[b] of 4 + 5, %	Olefin stereochemistry of 4
4a	$-CO_2Et$	90	100% trans
4b	$-SC_6H_5$	67	50:50 trans:cis
4c	$-SOC_6H_5$	81	100% cis
4d	$-SO_2C_6H_5$	80	100% trans

[a] The carbethoxy group was introduced as the phosphonium Wittig reagent, while the sulfur groups were introduced *via* the lithio phosphonates. All reactions were performed in tetrahydrofuran under standard conditions. [b] These are isolated yields which have not yet been maximized. [c] Wittig-type reagents which contain an α-carbanion-stabilizing group usually give predominately trans stereoisomers. The exclusive cis stereochemistry for the phenyl sulfinyl case (**4c**) is quite dramatic and surprising. We are currently investigating the generality of cis stereochemistry from phenylsulfinylmethyl phosphonate carbanions.

of trans:cis isomers while the methyl vinyl ketone adduct **3c** was exclusively the trans cyclopropane. Nmr analysis of the crotonaldehyde adduct **3b** indicated a mixture of three cyclopropanes[9] in a ratio of 3:3:1.

The cyclopropane **3a** derived from acrolein can serve as an important relay compound in the synthesis of hydroazulenes containing an angular methyl group. To this end, selective Wittig reactions were carried out at the aldehyde carbonyl in order to construct divinylcyclopropane systems (eq 3). Treatment of **3a** with various monosubstituted Wit-



tig-type reagents at room temperature or below resulted in the production of a trans divinylcyclopropane **4** and a rearranged product **5** (see Table II). The hydroazulene system **5** is formed directly from the cis cyclopropane aldehyde **3**, while the more stable trans divinylcyclopropanes **4** survive the reaction conditions. When the trans cyclopropanes, which also contain a trans olefin (**4a,b,d**), are heated at 100–140° in a sealed tube (chloroform), they smoothly rearrange to the corresponding hydroazulene isomers **5**, in quantitative yield.

The stereochemical prerequisites for the divinylcyclopropane rearrangement were clearly manifested in the thermal behavior of the various sulfur-substituted divinylcyclopropanes **4b–d**. When an approximately 1:1 mixture of trans:cis alkenes of **4b** was heated at 100°, the trans alkene rearranged to **5b** in 50 hr, while the cis alkene remained unchanged.[11] The cis vinyl sulfoxide **4c** did not cleanly rearrange to the hydroazulene but instead gave a complex mixture when heated at 135° for 30 hr. The difficulties in the rearrangements of the cis alkenes **4b** and **4c** are presumably due to steric hindrance in the transition states.[12] The pure trans alkenes **4a** and **4d** quantitatively rearranged to the corresponding hydroazulenes below 140°, thus affording the latter systems in overall yields of 60% or better starting from ylide **2**.

Since the Cope rearrangement of substituted divinylcyclopropanes has been shown by Baldwin[12] and others to be stereospecific and since only one stereoisomeric hydroazulene is produced in our systems, we have assigned the relative stereochemistry of the angular methyl and the R group as being trans.[13]

In summary, our approach to functionalized hydroazulenes not only utilizes mild reaction conditions and provides for flexibility in substitution patterns, but its final step furnishes a crowning touch of stereospecificity. We believe that the above synthetic scheme, because of its efficiency and high overall yields, will be invaluable for the total synthesis of guaianolides and pseudoguaianolides.

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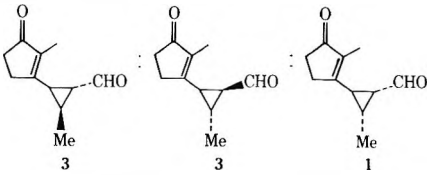
References and Notes

(1) Presented in part at the 6th Central Regional Meeting of the American Chemical Society, Detroit, Mich., April 22, 1974, Paper No. 207.
(2) J. S. Roberts, "Terpenoids and Steroids," Vol. 3, Specialist Periodical Reports, The Chemical Society, London, 1973, Chapter 2.
(3) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).
(4) For a recent review in this area, see J. A. Marshall, *Synthesis*, 517 (1972).
(5) (a) J. P. Marino and T. Kaneko, *Tetrahedron Lett.*, 3971 (1973); (b) *ibid.*, 3975 (1973).
(6) A recent report describes this compound and other vinyl halides: R. D. Clark and C. H. Heathcock, *Synthesis*, 47 (1974).
(7) All new compounds gave satisfactory elemental analyses (±0.3%). Nmr, ir and mass spectral data were all in agreement with the designated structures.
(8) Nmr ($CDCl_3$, ppm), 1.60 (s, 3 H), 2.33 (m, 2 H), 2.78 (m, 2 H), 3.44 (s, 6 H), 4.00 (broad s, 1 H); ir (KBr) 1620, 1515, 1045 cm^{-1}.
(9) The following structural assignments have been made for the crotonaldehyde adducts **3b** (see ref 5a).



(10) E. J. Corey and J. I. Shulman, *J. Org. Chem.*, **35**, 777 (1970); I. Shahak and J. Almog, *Synthesis*, 144 (1970); M. Mikolojczyk and A. Zatorski, *ibid.*, 669 (1973).
(11) The olefin stereochemistry was determined by the coupling constants for the vinyl protons in compounds **4a–c**, **4a** trans (J = 16 Hz), **4b** cis (J = 9 Hz), **4b** trans (J = 15 Hz), **4c** cis (J = 10 Hz).
(12) J. E. Baldwin and G. Ullenius, *J. Amer. Chem. Soc.*, **96**, 1542 (1974).
(13) A NOE experiment was performed at 100 MHz on a ~4% solution of **5a** in CCl_4. Saturation of the angular methyl protons enhanced the methine proton signal by 9%, indicating the angular methyl group and the methine proton were in close proximity.

Department of Chemistry
University of Michigan
Ann Arbor, Michigan 48104

Joseph P. Marino*
Takushi Kaneko

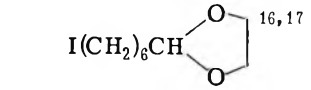
Received June 18, 1974

A General Synthesis of 1-Alkyl-1-cyclopentene-*cis*-3,5-diols. Useful Intermediates in Prostaglandin Synthesis

Summary: A simple one-step conversion of sulfoxides **2a** or **2b** to cis diols of general structure **1** is reported.

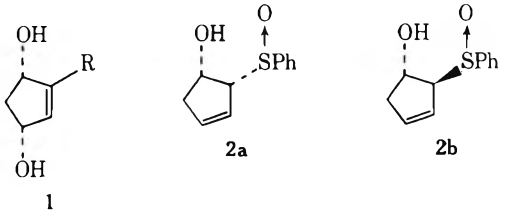
Sir: Advances in prostaglandin synthesis have resulted in the development of some highly ingenious approaches to this class of hormones.[1,2] Several years ago we initiated

Table I
1-Alkyl-1-cyclopentene-*cis*-3,5-diols 1[5,7]

R–X[a]	% yield 2[b]	Mp (bp), °C[c]
$I(CH_2)_5CH_3$	50–60 (70–77)	(75, 5 × 10^{-3} mm)
 [16,17]	54 (63)	51–52.5
$I(CH_2)_6CO_2$-*t*-Bu[18]	45 (57)	(110, 0.01 mm)
$BrCH_2C{\equiv}C(CH_2)_3CO_2$-*t*-Bu[19]	33 (48)	(60, 5 × 10^{-3} mm)
$BrCH_2C_6H_5$	50	95–96.5
$BrCH_2CH{=}CHC_6H_5$	(64)	103–105

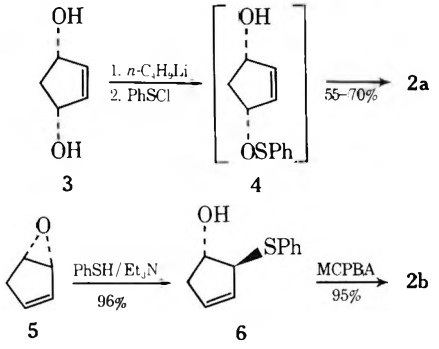
[a] See reference for mode of synthesis. [b] Yields in parentheses determined by nmr; all others are of purified product. [c] Values in parentheses are conditions employed for molecular distillation.

work on a general approach to the synthesis of allylic alcohols which would be amenable to the stereoselective synthesis of 1-alkyl-1-cyclopentene-*cis*-3,5-diols **1**.[3] Various derivatives of **1** may be readily perceived to be useful precursors to prostaglandins of both the E and F type.[4] This communication outlines a general approach to the stereoselective synthesis of *cis*-cyclopentenediols **1** which employs the hydroxy sulfoxides **2a** or **2b** as complementary precursors.



Synthesis of both the *cis*- and *trans*-hydroxy sulfoxides **2a** and **2b** was readily accomplished by the two routes outlined in Scheme I.[5] The cis isomer **2a** was prepared by

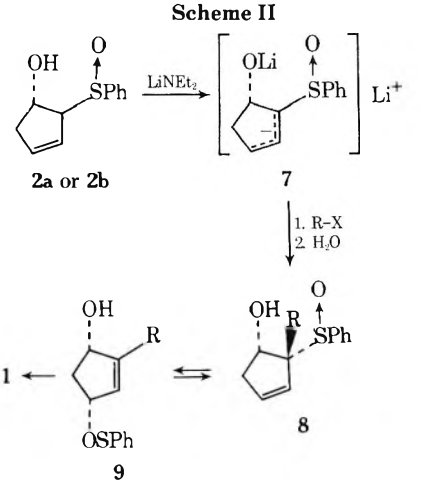
Scheme I



treatment of a 0.25 *M* solution of **3**[6] in dry tetrahydrofuran (THF) with 1 equiv of *n*-butyllithium (hexane) at −60° followed by titration with phenylsulfenyl chloride (~1.25 equiv) until the persistence of a yellow color. The resulting sulfenate ester **4** was allowed to rearrange to the *cis*-hydroxy sulfoxide **2a** at −20 to +5° over a 1.5-hr period. Sublimation of the product (95°, 0.05 mm) afforded **2a**, mp 102–112°, in 55–70% yield.[7,8] The relatively slow rate of rearrangement of **4** as compared to the analogous rearrangement of noncyclic sulfenate esters[3,9] is noteworthy. Synthesis of the *trans*-hydroxy sulfoxide **2b** was accomplished, in two steps in an overall yield of 91% starting from epoxycyclopentene (**5**).[10] Treatment of a 2.5 *M* solution of **5** in dry benzene at 0° with 1 equiv each of thiophenol and triethylamine followed by stirring at 25° for 4 hr afforded *exclusively* the *trans*-hydroxy sulfide as a homogenous liquid (molecular distillation; 90°, 0.05 mm) in 96% yield.[7] The observed regiospecific cleavage of epoxide **5** with a variety of mercaptide nucleophiles appears to be general. This result is in marked contrast to the capricious behavior of **5**, as well as other α,β-unsaturated epoxides, toward other nucleophiles.[10,11] Oxidation of **6** to the *trans*-hydroxy sulfoxide **2b** was carried out with *m*-chloroperbenzoic acid (CH_2Cl_2, 0°) in 95% yield.[5] Sublimation (90°, 10^{-5} mm) afforded a nicely crystalline solid, mp 96–113°.[7,8] Since both **2a** and **2b** are hygroscopic, care must be exercised in handling these compounds in subsequent experiments requiring anhydrous conditions.

The general approach for the conversion of either the *cis*- or *trans*-hydroxy sulfoxides **2a** or **2b** to the substituted cis diols **1** (Scheme II) deserves comment. *A priori* it was not known whether **2a** and **2b** would produce the same carbanion **7** upon metalation since some controversy exists in the literature on the pyramidal stability of α-sulfinyl carbanions.[12] Since the stereochemical course of the alkylation step (*cf.* **7** → **8**) could be influenced not only by substrate steric factors but also by carbanion geometry, it is interesting to note that alkylation appears to proceed only to give **8** and thus the cis diol **1**. These results suggest that the α-sulfinyl carbanion **7** is either planar or is undergoing pyramidal inversion prior to alkylation. On the other hand kinetic protonation of **7** results in the formation of *trans*-hydroxy sulfoxide **2b**. The observed high regioselectivity toward alkylation α to the phenylsulfinyl moiety (*cf.* **7** → **8**) appears to be characteristic of other phenylsulfinyl cycloalkenyl carbanions as well.[3,13]

Scheme II



The following general procedure is representative for the transformation of **2a** or **2b** to the substituted cis diols **1**. To a cooled (−40°) solution of 3.3 mmol of lithium diethylamide (from butyllithium and diethylamine) in 10 ml of dry THF under nitrogen is added 1–1.5 ml of dry hexamethylphosphoramide followed by 1.5 mmol of **2a** or **2b** in 4 ml of THF with stirring. The deep red solution of anion **7** is stirred for 30 min at which time the alkyl halide, R–X (1.6 mmol), is added either as a neat liquid or in a minimum volume of THF. Stirring is continued for an additional 30 min at −40° and 2 ml of a 50% aqueous solution of diethylamine is added to the reaction. The cold bath is removed and the reaction mixture is allowed to warm to room temperature and stirred ~2 hr to effect rearrangement and cleavage of **8** to the cis diol **1**. The cis diols **1** listed in Table I are purified by chromatography on neutral alumina (activity III).[5,7] The cis-diol stereochemistry is readily assigned by examination of the ^{1}H nmr chemical shifts and splitting patterns of the C-4 methylene protons.[14]

This approach to substituted, dioxygenated cyclopentenes differs from the alternate synthesis of such derivatives obtained *via* singlet oxidation of alkylcyclopentadienes[15] in one significant aspect. The inherent design of this reaction sequence affords the possibility of obtaining chiral cyclopentenediols **1** from precursors that may be chemically resolved. We are presently engaged in executing this idea and are developing methods for the elaboration of **1** to optically active prostanoids in the E and F series.

Acknowledgment. We wish to thank the Camille and Henry Dreyfus Foundation and the A. P. Sloan Foundation for unrestricted research support.

References and Notes

(1) For recent reviews, see P. H. Bentley, *Chem. Soc. Rev. (London)*, **2**, 29 (1973); U. Axen, J. E. Pike, and W. P. Schneider in "The Total Synthesis of Natural Products," Vol. 1, J. ApSimon, Ed., Wiley-Interscience, New York, N. Y., 1973, pp 81–142; N. M. Weinshenker and N. H. Anderson in "The Prostaglandins," Vol. 1, P. W. Ramwell, Ed., Plenum Press, New York, N. Y., 1973, pp 5–82.
(2) For recent synthesis not covered in ref 1, see R. C. Kelly, V. Van Rheenan, I. Schletter, and M. D. Pillai, *J. Amer. Chem. Soc.*, **95**, 2746 (1973); C. J. Sih, J. B. Heather, G. P. Peruzzotti, P. Price, R. Sood, and L. H. Lee, *ibid.*, **95**, 1676 (1973); R. B. Woodward, J. Gosteli, I. Ernst, R. J. Friary, G. Nestler, H. Raman, R. Sitrin, Ch. Suter, and J. K. Whitesell, *ibid.*, **95**, 6853 (1973); E. J. Corey and G. Moinet, *ibid.*, **95**, 6831, 6832 (1973); J. J. Partridge, N. K. Chadha, and M. R. Uskokovic, *ibid.*, **95**, 7171 (1973); J. S. Bindra, A. Grodski, T. K. Schaaf, and E. J. Corey, *ibid.*, **95**, 7522 (1973).
(3) For a general review, see D. A. Evans and G. C. Andrews, *Accounts Chem. Res.*, **7**, 147 (1974).
(4) For one approach to the further elaboration of the C_{13}–C_{20} side chain from a cyclopentenediol derivative, see E. J. Corey and T. Ravindranathan, *J. Amer. Chem. Soc.*, **94**, 4013 (1972).
(5) Detailed experimental procedures will be provided upon request for all reactions reported herein.
(6) G. O. Schenck and D. E. Dunlap, *Angew. Chem.*, **68**, 248 (1956).
(7) Satisfactory elemental analyses and spectral data were obtained on all compounds reported.
(8) Both **2a** and **2b** were prepared as a mixture of sulfoxide diastereoisomers. Stereochemical assignments are based upon mode of synthesis.
(9) V. Rautenstrauch, *Chem. Commun.*, 526 (1970).
(10) M. Korach, D. R. Nielson, and W. H. Rideout, *Org. Syn.*, **42**, 50 (1962). The filtered benzene solution of crude epoxycyclopentadiene **5** obtained in this procedure may be treated with thiophenol–triethylamine to give **6** directly in 64% yield.
(11) J. K. Crandall, D. B. Banks, R. A. Colyer, R. J. Watkins, and J. P. Arrington, *J. Org. Chem.*, **33**, 423 (1968); J. Staroscik and B. Rickborn, *J. Amer. Chem. Soc.*, **93**, 3046 (1971); C. R. Johnson and D. M. Wieland, *ibid.*, **93**, 3047 (1971); K. B. Sharpless and R. F. Lauer, *ibid.*, **95**, 2697 (1973); C. B. Rose and S. K. Taylor, *J. Org. Chem.*, **39**, 578 (1974).
(12) M. B. D'Amore and J. I. Brauman, *J. Chem. Soc., Chem. Commun.*, 398 (1973); R. Viau and T. Durst, *J. Amer. Chem. Soc.*, **95**, 1346 (1973); K. Nishihata and M. Nishio, *J. Chem. Soc., Perkin Trans. 2*, 1730 (1972).
(13) D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells. *Tetrahedron Lett.*, 1385 (1973).
(14) F. G. Cocu, G. Wolczunowicz, L. Bors, and Th. Posternak, *Helv. Chim. Acta*, **53**, 739 (1970). In **1** (R = $CH_2C_6H_5$) the ^{1}H nmr chemical shifts of the C-4 protons ($CDCl_3$) are at δ 2.60 (five-line multiplet) and 1.58 (doublet of triplets). The corresponding protons in **3** appear at δ 2.66 and 1.51.
(15) C. H. Sih, R. G. Salomon, P. Price, G. Peruzzoti, and R. Sood, *J. Chem. Soc., Chem. Commun.*, 240 (1972).
(16) Prepared from methyl 7-bromoheptanoate[17] by reduction with diisobutylaluminum hydride, ketalization, and halide exchange (69% overall yield).
(17) D. E. Ames, R. E. Bowman, and R. G. Mason, *J. Chem. Soc.*, 174 (1950).
(18) Prepared by the alkylation of the lithium enolate of *tert*-butyl acetate with 1,5-dibromopentane followed by halide exchange (50% overall yield).
(19) For a general approach, see J. Martel and E. Toromanoff, *Chem. Abstr.*, **76**, 24712d (1972).
(20) Camille and Henry Dreyfus Teacher-Scholar Recipient (1971–1976); Alfred P. Sloan Fellow (1972–1974). Address correspondence to Department of Chemistry, California Institute of Technology, Pasadena, Calif. 91109.
(21) Chancellor's Teaching Fellow, University of California, Los Angeles, Calif.

Contribution No. 3327
Department of Chemistry
University of California
Los Angeles, California 90024

D. A. Evans*[20]
T. C. Crawford[21]
T. T. Fujimoto
R. C. Thomas

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Singlet Oxygen Oxidation of Phosphites to Phosphates[1]

Summary: Singlet oxygen is shown (by means of Stern–Volmer analysis using β-carotene) to oxidize trialkyl phosphites to trialkyl phosphates in quantitative yield; relative rates of reaction are given for several phosphites.

Sir: We wish to report the dye-sensitized photooxidation of several trialkyl phosphites and the compelling evidence that the active oxidizing agent is singlet molecular oxygen.

Several trialkyl phosphites were irradiated with visible light[2] in acetone solution in the presence of Rose Bengal (RB)[3] while oxygen was bubbled through the solution continuously. In each case, the phosphate was formed in good yield as the only detectable product; the results are summarized in Table I. No reaction occurred in the dark or in the absence of dye.

Table I

Compound	Yield,[a] %	k_{rel}[b]	k_1, l. mol^{-1} sec^{-1}[c]
$(MeO)_3P$	85.4	0.65	1.52×10^7
$(EtO)_3P$	87.9	1.00	2.45×10^7
$(i\text{-}PrO)_3P$	66.2		
$(n\text{-}BuO)_3P$	82.4	0.78	
$(c\text{-}C_6H_{11}O)_3P$	83.0	0.60	
$(CH_2{=}CHCH_2O)_3P$	69.5		

[a] Products isolated by distillation or chromatography and crystallization, and identified by boiling point or melting point and ir comparison to authentic samples. [b] Determined by parallel irradiations using RB in acetone. [c] Determined by means of Stern–Volmer plot, employing MB, β-carotene, and benzene–methanol, 4:1 (v:v).

Although phosphites can be oxidized by ground-state oxygen in a photoinitiated free radical chain process,[4] the dye-sensitized photooxidation was only slightly retarded by

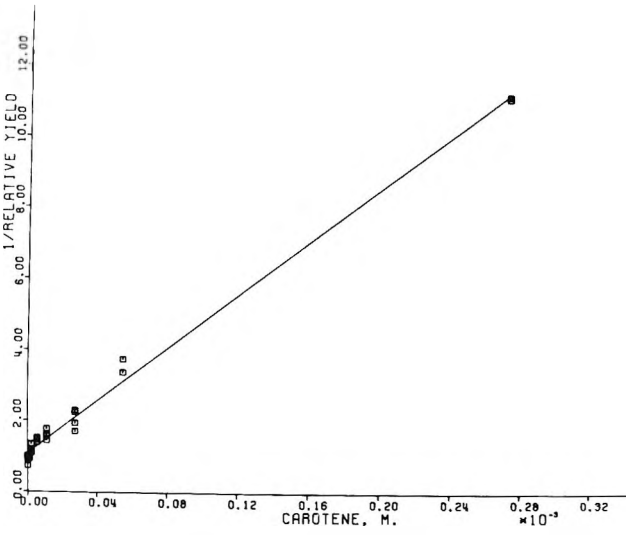

Figure 1. Stern–Volmer plot of β-carotene quenching of the photooxidation of trimethyl phosphite, 0.051 M in benzene–methanol (4:1 by volume) using Methylene Blue sensitizer.

the addition of hydroquinone, as expected for a singlet oxygen oxidation.[5] The intermediacy of singlet molecular oxygen in dye-sensitized photooxidations has frequently been inferred from competition between the substrate and known singlet oxygen acceptors, or from the observation of an identical reaction brought about by singlet oxygen formed by nonphotochemical means.[6] Such methods are inapplicable in this case, since phosphites are oxidized by the oxidation products (hydroperoxides and endoperoxides) of the usual singlet oxygen acceptors and also by the reactants (hydrogen peroxide, phosphite ozonides) usually used to prepare singlet oxygen in the dark.[7] Therefore we turned to the specific quenching by energy transfer of singlet oxygen by β-carotene and by 1,4-diazabicyclo[2.2.2]octane (Dabco).[5,6] Phosphate formation was quenched cleanly by both quenchers, and linear Stern–Volmer plots (see Figure 1) were observed in every case attempted. Singlet oxygen is thus confirmed as the oxidizing agent in this reaction.

The most attractive reaction mechanism is shown in Scheme I. The lack of reversibility of step 4 was shown by a linear plot of relative ϕ^{-1} (phosphate) *vs.* [phosphite]$^{-1}$, but the possibility of quenching by phosphite cannot be eliminated. Since k_d for singlet oxygen and the rate constants for β-carotene quenching of singlet oxygen are known for the solvent used, the rates of step 4 can be obtained from the slopes of the Stern–Volmer plots and are included in Table I. These rates are comparable to the rates of reaction of singlet oxygen with tetrasubstituted olefins and correlate with the electron-releasing ability of the alkoxy groups.

Scheme I

			Rate
1.	$^1RB + h\nu$	$\longrightarrow$ $^1RB^*$	I_0
2.	$^1RB^*$	$\longrightarrow$ $^3RB^*$	k_{isc}
3.	$^3RB^* + {}^3O_2$	$\longrightarrow$ $^1RB_0 + {}^1O_2$	k_s
4.	$(RO)_3P + {}^1O_2$	$\longrightarrow$ $(RO)_3P{\cdot}O_2$ (1)	k_1
5.	$1 + (RO)_3P$	$\longrightarrow$ $2(RO)_3PO$	k_2

The structure of the intermediate 1 cannot be deduced from the information available at this time. An intermediate of the same stoichiometry was proposed for the direct oxidation of phosphites and phosphines by phosphite ozonides,[8,9] and similar intermediates were proposed for the singlet oxygen oxidations of disulfides[10] and sulfides.[11] In the latter case, a zwitterionic structure (R_2S^+–O–O^-) was suggested based on solvent effects. A similar intermediate may be expected in the photooxidation of phosphites.

We are continuing to explore the scope of this reaction and seeking evidence for the structure of the intermediate.

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References and Notes

(1) Taken in part from the Ph.D. dissertation of P. R. Bolduc.
(2) A bank of 16 white fluorescent lamps, General Electric F15T8-W, were used as the light source; a merry-go-round was used in relative quantum yield experiments.
(3) Other solvents and Methylene Blue (MB) sensitizer were used with similar results.
(4) (a) J. I. G. Cadogan, M. Cameron-Wood, and W. R. Foster, *J. Chem. Soc.*, 2549 (1963); (b) J. B. Plumb and C. E. Griffin, *J. Org. Chem.*, **28**, 2908 (1963).
(5) C. S. Foote, R. W. Denney, L. Weaver, Y. Chang, and J. Peters, *Ann. N. Y. Acad. Sci.*, **171**, 139 (1970).
(6) D. R. Kearns, *Chem. Rev.*, **71**, 395 (1971).
(7) W. Gerrard and H. R. Hudson in "Organic Phosphorus Compounds," Vol. V, G. M. Kosalapoff and L. Maier, Ed., Wiley-Interscience, New York, N. Y., 1973, pp 21–329.
(8) Q. E. Thompson, *J. Amer. Chem. Soc.*, **83**, 845 (1961).
(9) E. Koch, *Tetrahedron*, **26**, 3503 (1970).
(10) R. W. Murray and S. L. Jindal, *J. Org. Chem.*, **37**, 3516 (1972).
(11) C. S. Foote and J. W. Peters, *J. Amer. Chem. Soc.*, **93**, 3795 (1971).
(12) Reilly Tar and Chemical Corp., Indianapolis, Ind. 46204.

University of Notre Dame **Paul R. Bolduc**
Notre Dame, Indiana 46556 **Gerald L. Goe***[12]

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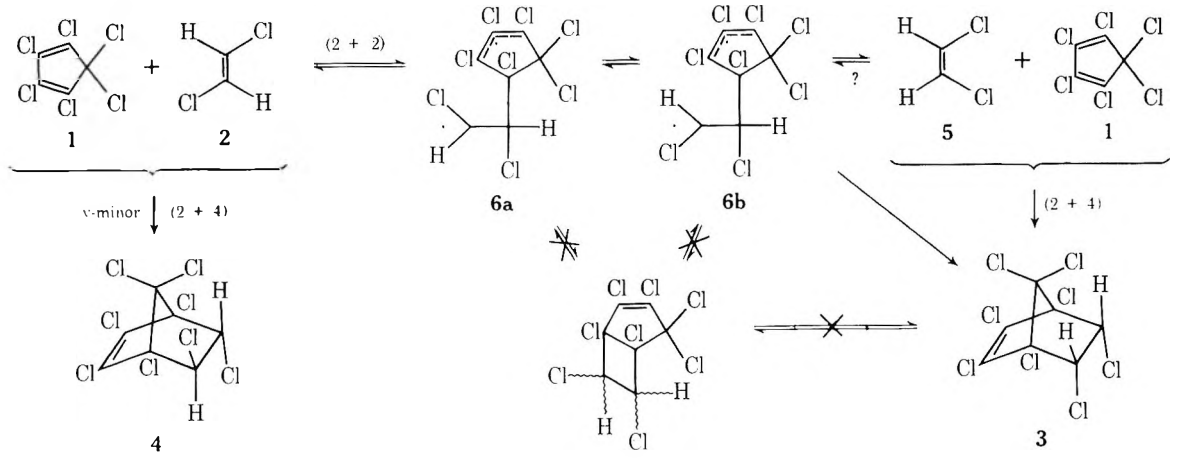
Nonstereospecific Diels–Alder Reactions. I. Reaction of Hexachlorocyclopentadiene with 1,2-Disubstituted Ethylenes

Summary: The Diels–Alder reaction of hexachlorocyclopentadiene and related dienes with a variety of trans-substituted ethylenes takes place with partial to extensive, *de facto* violation of the cis principle, including in one instance the loss of the structural integrity of the dienophile; two concurrent mechanisms, one involving concerted cycloaddition and the other biradical intermediates, are considered for the products.

Sir: The immense success of the Diels–Alder reaction in synthesis is due to a great extent to its stereospecificity whereby the steric integrity of the reactants is preserved in the adducts. This behavior, known as the cis rule, is considered to be the cardinal stereochemical principle of the Diels–Alder reaction.[1] We wish to report now on an extensive series of Diels–Alder reactions of hexachlorocyclopentadiene (1) in which the steric integrity of the dienophile was lost in the adduct, often extensively, in a clear, *de facto* violation of the cis rule.

To develop a rationale for the failure of 1 to form a Diels–Alder dimer on heating,[2] a possible result of steric hindrance between the chlorines of the incipient bridge and the exo positions, we investigated the reaction of 1 with *trans*-1,2-dichloroethylene (2). Heating the pure reactants

Scheme I



in equimolar proportions in a stirred, closed glass container for 67 hr at 163–165° yielded in 47% conversion an adduct which consisted of 95% of *cis-endo*-octachloronorbornene (**3**, mp 190–192°)[3] and 5% of the trans isomer (**4**).[3] The unreacted olefin contained 39% of *cis*-dichloroethylene (**5**).[4,5]

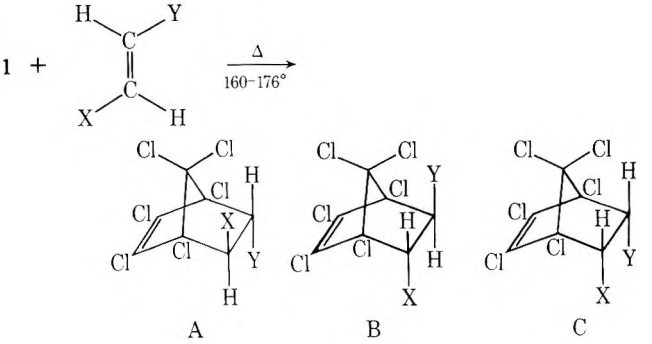
Heating **1** with equimolar amount of **5** at 163–165° for 62 hr gave in 62% conversion a product which consisted of 99.9% of **3** and 0.1% of *cis-exo*-octachloronorbornene (mp 96–98°).[3a,b] The unreacted olefin contained only the amount of **2** that was originally present (2%) in **5**.

Control experiments with neat **2**, **3**, **4**, and **5** showed that, when heated separately, neither of them underwent any isomerization under the above conditions. Even in the presence of HCl gas, a possible by-product and catalyst, **2** failed to yield any **5** at all at 165°. Since **2** underwent isomerization only in the presence of **1**, it is tempting to postulate that the two reactants formed a biradical intermediate akin to the free radicals invoked in the neat[7] or iodine[8] and benzoyl peroxide[8c] catalyzed isomerization of **2** and **5**.[9] Scheme I is proposed to account for the products.

While in Scheme I **3** can most simply be derived from **1** and **5** by the (2 + 4) cycloaddition process, the diastereomeric biradical **6b**, whose intermediacy *is* necessary for the isomerization of the olefin,[10] could also conceivably yield **3** directly by a simple coupling mechanism.[13] Although our present data do not allow a gauging of the energy requirements of the various steps (concerted 2 + 4 addition, biradical formation, radical epimerization, β scission, and ring closure), the latter three processes certainly have considerably lower energy requirements than the first two, and at the relatively high temperature of the reaction they readily could occur. The formation of **3** by a dual pathway thus appears permissible. However, competition between the facile steps of **6b** still could yield preferentially the β scission rather than coupling product.[14] The data also suggest that steric repulsion is the major underlying cause for the loss of the stereochemical integrity of the dienophile in the adduction process.[16,17] This view is supported by examples in which steric hindrance is reduced. Thus **2** yielded with 5,5-dimethoxytetrachlorocyclopentadiene (**7**) and tetrachlorofuran (**8**) only 10 and 5% of cis adducts, respectively, while with cyclopentadiene **2** yields only the trans adduct.[13a,21] Consonant with these results, **1**, **7**, and **8** produced with **5** increasingly more exo-cis adducts, 0.1, 2.0 and 9.4%, respectively, further confirming the effect of the incipient norbornene bridge on the stereochemistry of the adducts.

The loss of the stereochemical integrity of the dienophile in the formation of thermal adducts with **1** was encountered in various degrees with a multitude of other olefins (Table I), with 5-methylpentachlorocyclopentadiene and, to a lesser extent, with **7** and **8** as the dienes as well.

Table I
Distribution of Isomers in Adducts of 1 with Trans Olefins



X	Y	Composition of adducts, % A	B	C
CN	CN	57	..	43
$COOCH_3$	$COOCH_3$	73	..	27
COCl	COCl	84	..	16
Ph	Ph	71	..	29
CH_3	CH_3	~100	..	~0
CH_3	$COOCH_3$	84	4	12
CH_3	Ph	74	20	6
CH_3	COCl	23	3	74
CH_3	CN	12	31	57
CH_3	Cl	30	13	57
CH_2Cl	Cl	13		38[a]
Ph	Cl	5	14	81

[a] Adduct contained also 49% of 1,2,3,4,7,7-hexachloro-5-*endo*-(dichloromethyl)norbornene.

With allylic trans olefins as dienophiles, not only their stereochemical but also their structural integrity may be lost in the adduction process. Thus, while *trans*-1-chloropropene (**9**) and **1** yielded adducts differing only in stereochemistry, the adducts of **1** and *trans* 1,3-dichloropropene (**10**) contained structurally isomeric products as well (Table I). Neither **9** nor **10** showed any sign of isomerization when heated separately at the same temperature range in control experiments. A scheme analogous to that outlined above can account both for the stereochemical and structural isomerization of the olefins, and, consequently, for the structure of the adducts as well.

References and Notes

(1) (a) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961); (b) R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes." Interscience, New York, N.Y., 1964, p 908; (c) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **5**, 211 (1966); **6**, 16 (1967); (d) A. Wassermann, "The Diels–Alder Reaction," Elsevier, Amsterdam, 1965, p 24.

(2) (a) V. Mark and E. D. Weil, *J. Org. Chem.*, **36**, 676 (1971); (b) E. T. McBee, W. L. Dilling, and H. P. Braendlin, *ibid.*, **28**, 2255 (1963).

(3) (a) V. Mark, 156th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1968, Abstract ORGN-92; (b) V. Mark, Chlorocarbon Conference, Wayland, Mass., May 1968; (c) D. I. Davies and M. J. Parrott, *J. Chem. Soc. C*, 659 (1970).

(4) Since **2** contained 0.7% of **5**, 19.9% of it underwent isomerization.

(5) Although the reaction of **1** and **2** at 190–210° for 48 hr was claimed to give **4**,[6a] repetition of the experiment yielded aromatic breakdown products only.[3c] The products of another experiment at 200° were not identified.[6b] A 37.7% yield of **3** was secured when **1** was heated at 200° with a 9:1 mixture of **5** and **2**.[3c]

(6) (a) B. A. Arbuzov and A. N. Vereshchagin, *Bull. Acad. Sci. USSR*, 586 (1965); (b) E. T. McBee, H. Rakoff, and R. K. Meyers, *J. Amer. Chem. Soc.*, **77**, 4427 (1955).

(7) The neat thermal isomerization of **2** was shown to be not unimolecular but significantly accelerated by high temperature (275 to 391°): (a) B. S. Rabinovich and M. J. Hulatt, *J. Chem. Phys.*, **27**, 592 (1957); (b) C. Steel, *J. Phys. Chem.*, **64**, 1588 (1960).

(8) (a) R. E. Wood and R. G. Dickinson, *J. Amer. Chem. Soc.*, **61**, 3259 (1939); (b) K. S. Pitzer and J. L. Hollenberg, *ibid.*, **76**, 1493 (1954); (c) A. H. Ewald, S. D. Hamann, and J. E. Stutchbury, *Trans. Faraday Soc.*, **53**, 991 (1957).

(9) Although on heating at higher temperature (240–250°) **1** yields chlorine, chlorinated **1**, and various C_9, C_{15}, and C_{20} chlorocarbons presumably *via* a dissociative process involving $C_5Cl_5\cdot$ and $Cl\cdot$,[2] no products of these radicals were detected in the reaction mixtures of **1** with **2** or **5** at 165°, suggesting that these radicals are not involved in the isomerization of **2**. Furthermore, both **7** and **8**, which are less likely sources of radicals than **1**, also yielded significant amounts of cis adducts. Also, the presence of oxygen (air) had no apparent effect on the rate of isomerization, as did neither that of anhydrous potassium carbonate (to intercept HCl). Attempts to use conventional radical inhibitors, such as phenols and anilines, were frustrated by their high reactivity with **1**.

(10) Significantly, these reactions yielded no 2 + 2 adducts, which, based on the analogy of 1,2,3,4,4,5,6,7,7-nonachlorobicyclo[3.2.0]-2-nonene,[11] are thermally stable under the reaction conditions. The reason for their absence may well be due to the dominance of competing epimerization, β scission, and radical coupling processes of lower energy requirements,[12] resulting in **5**, and **3** as end products.

(11) A. Roedig and L. Hornig, *Justus Liebigs Ann. Chem.*, **598**, 208 (1956).

(12) The activation energy of biradical ring closure to a four-membered ring is considerably higher than that to a six-membered ring: (a) H. E. O'Neil and S. W. Benson, *Int. J. Chem. Kinet.*, **2**, 423 (1970); (b) R. G. Bergman in "Free Radicals," Vol. I, J. Kochi, Ed., Wiley, New York, N.Y., 1973, p 191.

(13) For a critical, in-depth review of 2 + 2 and 2 + 4 cycloadditions to conjugated dienes, see (a) P. D. Bartlett, *Science*, **159**, 833 (1968); (b) P. D. Bartlett, *Quart. Rev., Chem. Soc.*, **24**, 473 (1970).

(14) A monitoring of the products from the beginning indicates that in the reaction of **1** with **2** the rate of adduct formation (**3**) increases as the concentration of **5** increases. Since the rate of disappearance of **5** is higher than that of **2** in their reactions with **1**, the appearance of a sigmoid segment in the rate of formation of **3** in the latter reaction can readily be rationalized.[15]

(15) I thank a referee for his helpful comments, which elicited this and several other footnotes and references.

(16) These considerations do not apply, of course, when the olefins (*e.g.*, 1,2-dibromoethylene, *trans*-1,4-dichloro-2-butene) can undergo isomerization *per se* under the reaction conditions.

(17) The fact that, contrary to the conclusion of an earlier study,[6b] 1,1-dichloroethylene does yield a 2 + 4 adduct with **1**,[18] indicates that, if the reaction evolves stepwise, a biradical analogous to **6** can undergo ring closure to the octachloronorbornene, presumably because in the absence of competing isomerization steps ring closure to the 2 + 4 adduct remains its only forward option. Significantly, tetrachloroethylene does not yield an adduct with **1** under the above conditions, even though perchloronorbornene is a stable chlorocarbon, readily accessible by another route.[19] These olefins thus parallel the behavior of the sterically hindered systems described by Newman, for which he proposed that the Diels–Alder reaction can proceed by a stepwise mechanism.[20]

(18) V. Mark, *J. Org. Chem.*, **39**, 3181 (1974).

(19) V. Mark, unpublished results; *cf.* G. E. Hawkes, R. A. Smith, and J. D. Roberts, *J. Org. Chem.*, **39**, 1276 (1974).

(20) M. S. Newman, *J. Org. Chem.*, **26**, 2630 (1961).[15]

(21) J. B. Lambert and J. D. Roberts, *Tetrahedron Lett.*, 1457 (1965).

(22) Address correspondence to Engineering Polymer Products Department, General Electric Co., Mt. Vernon, Ind. 47620.

Hooker Research Center **Victor Mark**[22]
Niagara Falls, New York 14302

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Nonstereospecific Diels–Alder Reaction. II. Reaction of Hexachlorocyclopentadiene with 1,1-Disubstituted and Monosubstituted Ethylenes

Summary: The major epimers in the adducts of hexachlorocyclopentadiene, and related dienes, with unsymmetrical 1,1-disubstituted ethylenes are those in which the bulkier substituents are endo, irrespective of secondary orbital interaction considerations; similar results obtain with monosubstituted ethylenes as well, where the cyano and aldehydo substituents yield significant proportions of the novel exo adducts.

Sir: In the preceding communication we described the Diels–Alder reaction of hexachlorocyclopentadiene (**1**) with a variety of 1,2-disubstituted ethylenes, which takes place with a *de facto* violation of the cis principle, and suggested that steric hindrance may be the main underlying cause for the anomalous behavior.[1] To gain a better insight into the role of various substituents in these reactions, we examined the behavior of 1,1-disubstituted olefins as well.

The experiments were carried out by heating **1** with the olefin in a stirred and sealed, all glass system at the lowest temperature at which the reaction proceeded at a convenient rate and quantitatively analyzing the crude product by proton nmr before any subsequent separation, purification, and identification steps. To facilitate structure assignment, adducts of **1** with symmetrically 1,1-disubstituted ethylenes have also been prepared as model compounds; the pertinent 1,2,3,4,7,7-hexachloronorbornenes yielded the following nmr parameters: 5,5-dimethyl- (**2**) δ, H_{exo} 2.499, H_{endo} 1.963 ($J_{gem} = -13.0$ Hz), $CH_{3,exo}$ 1.50, $CH_{3,endo}$ 1.02; 5,5-diphenyl- (**3**), H_{exo} 3.633, H_{endo} 3.158 ($J_{gem} = -13.6$ Hz); 5,5-dichloro- (**4**), H_{exo} 3.497, H_{endo} 3.114, ($J = -14.7$ Hz), $CDCl_3$ solution. Isomer distribution data in adducts of representative, 1,1-dissimilarly substituted ethylenes are shown in Table I.

The results of these kinetically controlled[2] experiments indicate the following competitive relationships for the less hindered endo position.

$$(CH_3)_2CH > CH_3CH_2 > H_3C$$

$$CH_3OOC \sim Cl \sim Ph \gg H_3C \sim ClCH_2 \sim CHO > CN$$

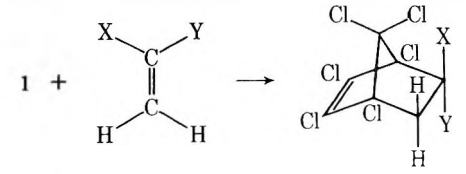
$$Cl \gg CH_3OCH_2 > H_3C$$

While the alkyl series underlines the role of size in the competition, and it apparently can be extended to include the aldehydo and cyano substituents, several of the cases reflect the results of opposing forces. Thus, while secondary orbital interaction[3] between the π system of **1** and the dienophile can be invoked with phenyl, methoxycarbonyl, and perhaps even chlorine,[4] to rationalize their endo selectivity, it cannot account for the preferentially exo pattern of the aldehydo and cyano substituents.[5] However, size and secondary attractive forces, when considered jointly, seem to accommodate the results. When in competition, size appears to dominate over secondary interactions (methyl *vs.* the planar aldehydo and the linear nitrile substituents) and, expectedly, the two effects reinforce each other when not in opposition (phenyl *vs.* methyl).[6]

The results of the reaction of **1** with α-methylstyrene (**5**) differ from literature data in two respects.

(a) The structure assigned[7] to the crystalline adduct[8] (**6A**) of **1** and **5** had the phenyl group exo and was derived from the nmr spectrum of its deuterium-labeled analog based on the assumption that the exo proton resonates downfield from the endo proton. Exact repetition of the reaction conditions[7] yielded in our hands a crystalline ad-

Table I
Distribution of Isomers in Adducts of 1 with Unsymmetrically 1,1,-Disubstituted Ethylenes[a]



X	Y	%	Y_{endo}/Y_{exo}
CH_3	CH_3CH_2	64	1.8
CH_3	$(CH_3)_2CH$	85	5.7
CH_3	$ClCH_2$	45	0.8
CH_3	CH_3OCH_2	70	2.3
CH_3	C_6H_5	89	8.1
CH_3	OHC	48	0.9
CH_3	NC	24[b]	0.3
CH_3	CH_3OOC	92	11.5
CH_3	Cl	90[c]	9.0
C_6H_5	$ClCH_2$	10	0.1
C_6H_5	Cl	55[d]	1.2
CH_3OCH_2	Cl	81	4.3
NC	Cl	97	32.3
CH_3OOC	Cl	60	1.5
$BrCH_2$	Br	86	6.1

[a] The numerical values are the extent of the given isomers present in the adduct; hence they are not necessarily yield data. The other epimers are present in complementary percentages. [b-d] In the corresponding adducts of 7 the analogous epimer is present in 30, 89, and 56%, respectively.

duct as the major product, mp 67–69°, **6A**, whose nmr analysis, in $CDCl_3$, showed the methylene doublets (δ 2.67 and 3.15, J = −13.9 Hz), the methyl singlet (δ 1.88), and the closely bunched aromatic protons (δ 7.24). A comparison of these parameters with those of model compounds **2** and **3** indicates that the downfield doublet of **6A** coincides well with the upfield (endo) doublet of **3**, and the upfield doublet of **6A** matches closely the downfield (exo) doublet of **2**. The converse matching for the epimeric adduct **6B** (δ H_{exo} 3.495, H_{endo} 2.125, J = −13.2 Hz, CH_3 1.375, Ph 7.1–7.4 and 7.5–7.66, multiplets) plus the fact that the methyl peak of **6A** is more deshielded than that of **6B**, indicate that in the major adduct, **6A**, the methyl group is exo[9] (Figure 1).

(b) The reaction of **5** with **1** yields not one, but two epimeric adducts. As such, it is not exo/endo stereospecific, as is neither its reaction with 5,5-dimethoxytetrachlorocyclopentadiene (**7**) and tetrachlorofuran (**8**), which yield 88 and 80%, respectively, of the analogs of **6A**. In fact, none of the reactions of Table I are completely stereospecific.[10]

The data of Table I suggest that the sterically least demanding aldehydo and cyano substituents are forced in the sterically unfavored exo position when they are in competition with bulkier substituents. To evaluate them against the smallest of substituents, several monosubstituted ethylenes were allowed to react with **1** and the adducts analyzed for isomeric composition.

As anticipated, the halogens and bulky carbon substituents, such as *tert*-butyl, phenyl, and methoxycarbonyl yielded endo adducts only, but propylene, acrolein, and acrylonitrile produced 5, 14, and 14%, respectively, of the exo products as well. With **1**, **7**, and **8**, acrylonitrile yielded increasingly more exo adducts, 14, 17 and 38%, respectively, providing thus additional support for the steric argument and suggesting again the relatively subordinated role of secondary orbital interaction in these reactions.

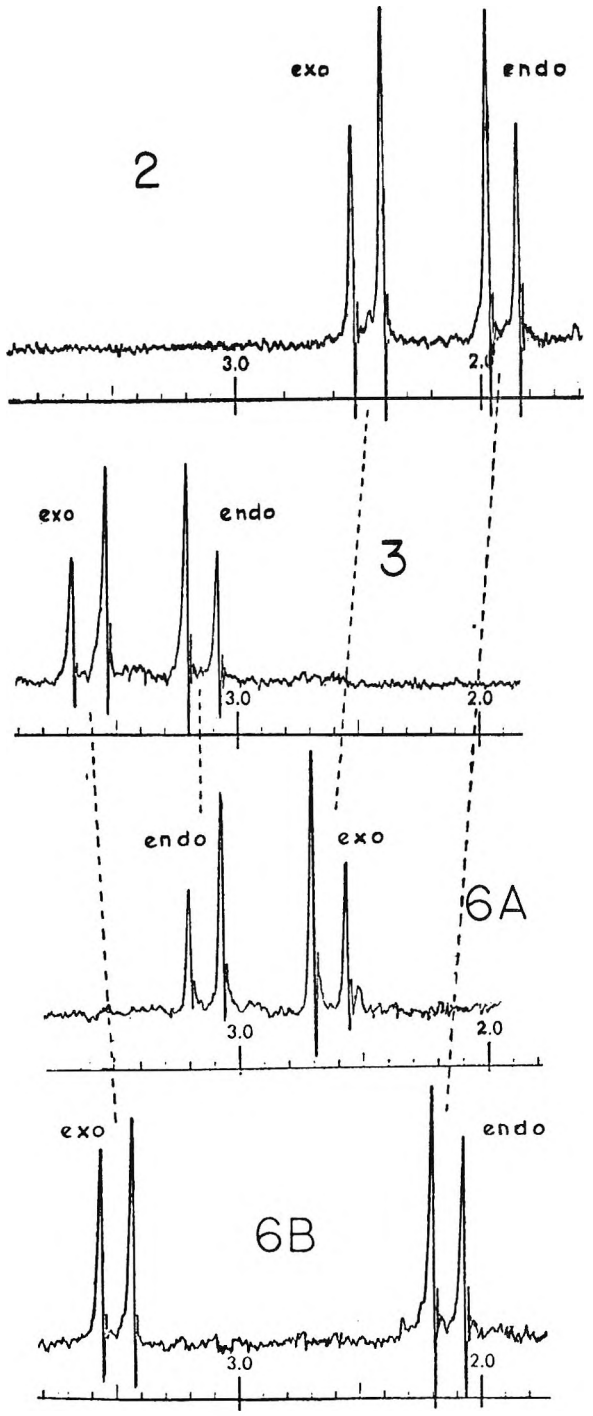


Figure 1. Pmr spectrum of the methylene protons in **2**, **3**, **6A**, and **6B**.

References and Notes

(1) V. Mark, *J. Org. Chem.*, **39**, 3179 (1974).
(2) As indicated by the theral stability of the isomerically pure adducts under reaction conditions.
(3) Which is the expression in quantum chemical terms of Alder's rule of maximum accumulation of unsaturation (endo rule): R. Hoffmann, and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4388 (1965).
(4) (a) K. L. Williamson, Y. L. Hsu, R. Lacko, and C. H. Youn, *J. Amer. Chem. Soc.*, **91**, 6129 (1969); (b) K. L. Williamson and Y. L. Hsu, *ibid.*, **92**, 7385 (1970).
(5) It is becoming increasingly more apparent from thoroughly investigated systems that, when not in competition with hydrogen, unsaturated substituents tend to violate the rule of endo addition in kinetically controlled Diels–Alder reactions: (a) J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Amer. Chem. Soc.*, **84**, 297 (1962); (b) ref 4; (c) Y. Kobuke, T. Fueno, and J. Furukawa, *J. Amer. Chem. Soc.*, **92**, 6548 (1970); Y. Kobuke, T. Sugimoto, J. Furukawa, and T. Fueno, *ibid.*, **94**, 3633 (1972); (d) K. N. Houk and L. J. Luskus, *ibid.*, **93**, 4606 (1971); (e) E. T. McBee, M. J. Keogh, R. B. Levek, and E. P. Wesseler, *J. Org. Chem.*, **38**, 632 (1973); (f) B. M. Jacobson, *J. Amer. Chem. Soc.*, **95**, 2579 (1973); (g) J. M.

Mellor and C. F. Webb, *J. Chem. Soc., Perkin Trans. 2*, 17, 26 (1974); B. C. C. Cantello, J. M. Mellor, and C. J. Webb, *ibid.*, 22 (1974).
(6) While a detailed analysis of the data is deferred to the full paper, several correlations emerge even from a cursory comparison with analogous nonchlorinated dienes. Thus, in both systems (a) increased size of the alkyl group enhances their endo selectivity;[5g] (b) increased steric bulk destabilizes both the endo and exo transition states;[1,5g] (c) repulsive nonbonding interactions between the diene and a bulky substituent seem to be the major cause for their endo selectivity;[1,5d,g] size and its unfavorable geometry for secondary overlap are probably responsible for the low endo selectivity of the nitrile group.[5g]
(7) J. B. Lambert and J. D. Roberts, *Tetrahedron Lett.*, 1457 (1965).
(8) J. Sauer, Habilitationsschrift, University of Munich, 1963, p 113.
(9) The assignment of the downfield doublet to the endo proton in **6A** is supported also by its line widths, which are somewhat broader than those upfield, thus suggesting a ^4J W-coupling with the methyl protons and, hence, a trans relationship. In epimer **6B** it is again the downfield doublet, assigned now to the exo proton that is broader in accordance with the proposed structure.
(10) The reaction of **1** and **5-*d*** is often quoted[11] in support of the concerted nature of the Diels–Alder reaction, which, although heavily weighted in favor of a biradical pathway, still yielded, reportedly, one cis/trans stereospecific adduct.[7] Although our finding that **6A** has the stereochemistry opposite to that proposed[12] does not invalidate the conclusion that the stereochemical integrity of the deuterium-labeled olefin was maintained in the adduct, the formation in significant proportion of **6B** weakens the validity of the argument in support of the mechanism of the Diels–Alder reaction until the cis–trans stereospecificity of **6B** is determined. Should, however, subsequent experiments establish, *e.g., via* similar deuterium labeling, the conservation of the steric integrity of the olefin in **6B** as well, the finding would reinforce the argument in favor of the one-step mechanism, since it would clearly underline the relevance of molecular alignment in the preadduction state.
(11) *Cf., inter alia*, (a) T. L. Gilchrist and R. C. Storr, "Organic Reactions and Orbital Symmetry," Cambridge University Press, London, 1972, p 97; (b) S. Seltzer in "Advances in Alicyclic Chemistry," H. Hart and G. J. Karabatsos, Ed., Academic Press, New York, N.Y., 1968, p 43; (c) J. Sauer, *Angew. Chem. Int. Ed. Engl.*, **6**, 16 (1967); (d) B. Capon, M. J. Perkins and C. W. Rees, "Organic Reaction Mechanisms," Interscience, New York, N.Y., 1965, p 123.
(12) The reversal of assignment in the stereochemistry of **6A** was not unanticipated.[7] While recognizing that it violated the endo rule, and done only reluctantly, the placement of the phenyl group in the exo position was necessary based on the then available chemical shift data, which indicated that, without exception, the endo methylene protons in adducts of **1** resonate at higher field.[7,13]
(13) Other examples where the endo methylene proton is not upfield from the exo include the adduct of **1** with 2-chloropropene (in the *exo*-methyl epimer), with *ar*-pentachloro- and *ar*-pentabromostyrene, and with α-methylacrylonitrile (where they are adventitiously equivalent in the exo methyl epimer in $CDCl_3$, but not in C_6D_6 solution).
(14) Address correspondence to Engineering Polymer Products Department, General Electric Co., Mt. Vernon, Ind. 47620.

Hooker Research Center **Victor Mark**[14]
Niagara Falls, New York 14302

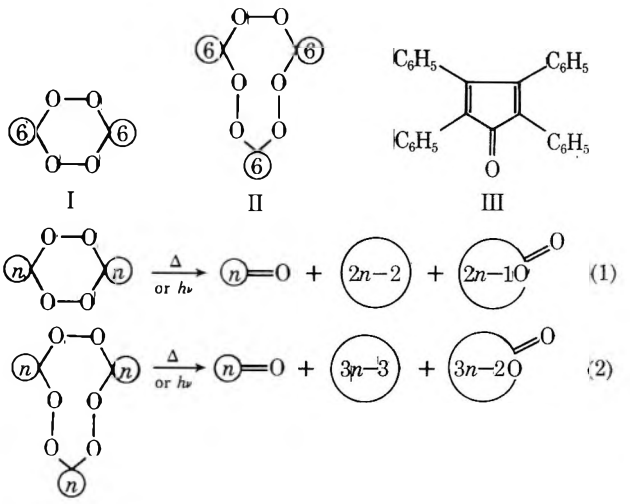
Received June 3, 1974

Singlet Oxygen Scavenger Method for the Determination of Ketone Peroxide Kinetics

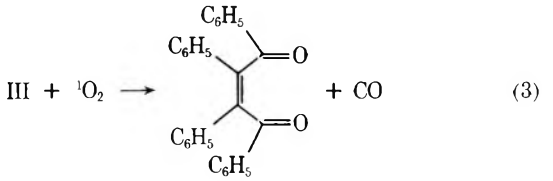
Summary: The rate of decomposition of dicyclohexylidene diperoxide (I) has been monitored spectrophotometrically by use of the colored singlet oxygen scavenger "tetracyclone" (III) (tetraphenylcyclopentadienone). The rate constants determined for I are in good agreement with those determined iodometrically.

Sir: In 1967 Story and coworkers[1] found that the thermal and photochemical decomposition of cyclic ketone peroxides such as I and II produced macrocyclic hydrocarbons and lactones (eq 1 and 2). About 5–10% ketone was also produced. Story suggested that the ketone was produced with the evolution of singlet oxygen.

The detection of singlet oxygen in liquid phases is restricted almost entirely to chemical methods which might be misleading (but several methods are available).[2-4] In order to determine the singlet oxygen in a liquid phase, one may decompose the precursor in the presence of an appropriate singlet oxygen acceptor.[5]



For example, Murray and coworkers used tetracyclone to measure the per cent of singlet oxygen evolved from ozone adducts of isopropyl alcohol and isopropyl ether (eq 3).[6] In our laboratory Brennan used tetracyclone to scavenge singlet oxygen from phosphorus ozone adducts.[7]



It occurred to us that this highly colored compound might be used (if thermally stable) to measure the singlet oxygen evolved from peroxide precursors. The extinction coefficient of this compound is high [$\epsilon \simeq 1250$ l./(mol cm)], thus allowing the singlet oxygen yields to be determined on dilute peroxide solutions with the aid of a spectrophotometer.

The stable free radical technique for the determination of free radical initiator kinetics had been so successful for the determination of the kinetics and free radical efficiencies of diacyl peroxides that we decided to apply the same technique to peroxides which might give singlet oxygen on decomposition.[8]

The advantages are (a) the solution of peroxide is dilute enough so that induced decomposition is negligible; (b) the rate constant and the efficiency of singlet oxygen production (the fraction of singlet oxygen per mole of peroxide which reacts with the scavenger) may be determined in a single experiment.

The rate data for the decomposition of cyclohexanone diperoxide obtained by monitoring the disappearance of the colored band at 510 mμ in tetracyclone were calculated from eq 4 and are presented in Table I (see ref 8 for derivation of a similar equation). The rate data are in good agreement with that obtained by following the rate iodometrically in all solvents except cyclohexane.[9] The reason for this discrepancy has not been completely resolved.

$$\ln (A - A_\infty) = -kt + \ln \varepsilon P_o e_s \quad (4)[10]$$

The values of e_s for I range from 0.05 to 0.02 in the solvents studied, and it appears that the peroxide is not an efficient source of singlet oxygen. The yield of cyclohexanone varies from 0.10 to 0.20 mol/mol of peroxide; so the maximum available singlet oxygen is 5 to 10% (0.05 to 0.10 for e_s). Furthermore, it is likely that the values of e_s recorded in Table I are too high since it is possible for the fading of

Table I
Kinetics and Singlet Oxygen Efficiencies for Dicyclohexylidene Diperoxide in Some Solvents[a]

Solvent	$10^3 P_0$, mol/l.[b]	$T°$, C	$10^5 k$ (± std dev), sec^{-1}	$t_{1/2}$, min	$t_{1/2}$, min[c]	e_s
Toluene	10.0	170.1	96.3 (±4.6)	12.0	13.2	0.038
	10.6	170.1	99.1 (±4.0)	11.6		0.035
	5.00	170.1	84.0 (±6.2)	13.7		0.039
	8.46	160.1	27.9 (±1.3)	41.4	39.6	0.048
	10.0	160.1	31.2 (±1.2)	37.0		0.035
	10.0	160.1	25.8 (±0.7)	44.7		0.044
	10.1	160.1	29.3 (±4.0)	39.4		0.035
Cyclohexane	10.0	160.1	23.5 (±1.3)	30.0	41.6	0.038
	10.0	155.1	14.6 (±0.7)	61.4	86.8	0.043
Chlorobenzene	10.0	155.1	27.4 (±2.8)	42.1	45.0	0.050
Bromobenzene	13.5	160.1	45.5 (±0.4)	25.4	26.2	0.046
	13.5	155.1	27.0 (±0.8)	42.8	45.0	0.049
o-Dichlorobenzene	10.0	160.1	36.0 (±1.9)	32.0		0.022
	10.0	155.1	27.3 (±1.4)	42.3		0.026
	10.0	150.0	18.0 (±2.0)	64.3		0.019
Acetophenone	10.0	155.1	27.8 (±0.6)	41.6	37.3	0.043

[a] The initial scavenger concentration (S_0) was 8.00×10^{-4} *M*. [b] Initial peroxide concentration in moles per liter. [c] The half-life in this column came from iodometric rate studies ($P_0 \simeq 0.02$ mol/l.).

the tetracyclone to be caused by addition of radicals to the double bonds (eq 5).

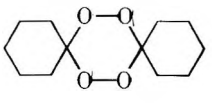
$$R\cdot + \text{III} \longrightarrow R - \text{III}\cdot \longrightarrow \text{colorless products} \quad (5)$$

When III was heated with di-*tert*-butyl peroxide in degassed chlorobenzene solution at 160°, fading occurred. This is presumably due to radical addition to the double bonds of III. No product studies were done however.

Table II shows the yield of *cis*-dibenzoylstilbene determined by vpc analysis. The yield is higher here than the yield determined spectrophotometrically.

It was observed in the vpc trace that there were several unidentified peaks with a retention time higher than those of *cis*-dibenzoylstilbene and tetracyclone. These peaks were shown to be absent when the peroxide was thermolyzed in the absence of tetracyclone. The products which give rise to the unidentified peaks are presumed to be radical addition products of tetracyclone.

It is likely that the oxygen which is generated in the thermal decomposition of ketone peroxides enters into a chain reaction[11] if it does not add to tetracyclone as singlet oxygen. For example, the following free radical chain process is reasonable.



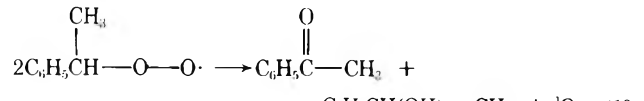
$$\longrightarrow \text{products} + R\cdot + O_2 \quad (6)$$

$$R\cdot + O_2 \longrightarrow R{-}O{-}O\cdot \quad (7)$$

$$R{-}O{-}O\cdot\ (R\cdot) + \text{tetracyclone} \longrightarrow \text{radical adduct} \quad (8)$$

$$R{-}O{-}O\cdot + R{-}O{-}O\cdot \longrightarrow \text{nonradical products} \quad (9)$$

The termination reaction 9 has been shown for the autoxidation of ethylbenzene to give the products in eq 10.[12] This type of termination is well known for secondary peroxy radicals.[12-15]



$$2C_6H_5CH(CH_3){-}O{-}O\cdot \longrightarrow C_6H_5C(=O){-}CH_3 + C_6H_5CH(OH){-}CH_3 + {}^1O_2 \quad (10)$$

The point to be made by eq 6 through 10 is that fading of the tetracyclone may be caused by radical addition (eq 8) or singlet oxygen generated *via* paths such as eq 9.

Table II
Per Cent Yield of *cis*-Dibenzoylstilbene

Solvent	$T°$, C	P_0, mol/l.[a]	S_0, mol/l.[b]	e_s[c]	e_s[d]
Cyclohexane	160	0.1	≃0.05	0.053	0.038
	170	0.1	≃0.05	0.078	
n-Decane	150	0.1	≃0.05	0.034	
	160	0.1	≃0.05	0.074	
Toluene	150	0.1	≃0.05	0.058	
	160	0.1	≃0.05	0.078	0.035–0.048
	170	0.1	≃0.05	0.099	0.035–0.039
Chlorobenzene	140	0.1	≃0.05	0.059	
	150	0.1	≃0.05	0.055	0.046
	160	0.1	≃0.05	0.055	
	165	0.1	≃0.05	0.053	

[a] Initial peroxide concentration in moles per liter. [b] Initial scavenger concentration in moles per liter. [c] Yield of *cis*-dibenzoylstilbene determined by vpc analysis. [d] Singlet oxygen efficiency determined by spectrophotometry on dilute solutions ($P_0 = 0.01$, $S_0 = 0.0008$ mol/l.).

Despite the number of interferences, the method presented above appears to be useful for determination of the rate of decomposition of peroxides such as I which are potential singlet oxygen precursors. Indeed, the above is only a fair demonstration of the method. Furthermore, very little was learned about that portion of the decomposition of I which gives cyclohexanone plus oxygen. However, the technique should be very useful for the determination of rates of decomposition and singlet oxygen efficiencies (e_s) in systems which give higher yields of singlet oxygen without the interference encountered in the study of I.

Acknowledgment. We thank the National Science Foundation for support of this work through Grant No. 34496.

References and Notes

(1) P. R. Story, D. D. Denson, C. E. Bishop, B. C. Clarke, Jr., and J. C. Farine, *J. Amer. Chem. Soc.*, **90**, 817 (1968).
(2) C. S. Foote, *Accounts Chem. Res.*, **1**, 104 (1968).
(3) W. Gergmann and H. J. McLean, *Chem. Rev.*, **28**, 367 (1941).
(4) W. Wilthey, S. Henkels, and M. Leonard, *J. Prakt. Chem.*, **151**, 97 (1938).

(5) G. O. Schenck and J. Hasselmann, *Z. Electrochem.*, **56**, 855 (1956).
(6) R. W. Murray, W. L. Lumma, Jr., and J. W. P. Lin, *J. Amer Chem. Soc.*, **92**, 3205 (1970).
(7) M. E. Brennan, *Chem. Commun.*, 956 (1970).
(8) R. C. Lamb and J. R. Sanderson, *J. Amer. Chem. Soc.*, **91**, 5034 (1969); R. C. Lamb and J. G. Padifici, *ibid.*, **86**, 914 (1964); R. C. Lamb, F. F. Rogers, Jr., G. C. Dean, Jr., and F. W. Voigt, Jr., *ibid.*, **84**, 2635 (1962).
(9) J. R. Sanderson and P. R. Story, *J. Org. Chem.*, in press.
(10) Here A is the absorbance at some maximum wavelength. A_∞ is the absorbance at infinity time, ϵ is the molar extinction coefficient, e_s is the singlet oxygen efficiency, and P_0 is the initial peroxide concentration.
(11) G. A. Russell, *J. Chem. Educ.*, **36**, 111 (1959).
(12) G. A. Russell, *J. Amer. Chem. Soc.*, **79**, 3871 (1957).
(13) J. A. Howard and K. U. Ingold, *J. Amer. Chem. Soc.*, **90**, 1056 (1968).
(14) P. D. Bartlett and J. G. Traylor, *ibid.*, **85**, 2407 (1963).
(15) J. E. Bennett, D. M. Brown, and B. Mile, *Trans. Faraday Soc.*, **66**, 386 (1970).
(16) Address correspondence to author at Story Chemical Corp., Ott Division, Muskegon, Mich. 49445.

Department of Chemistry **John R. Sanderson*[16]**
University of Georgia **Paul R. Story[16]**
Athens, Georgia 30601

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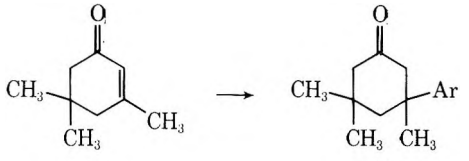
Heteroatom-Directed Photoarylation. A New Method for Introduction of Angular Carbon–Carbon Bonds

Summary: Photocyclization–rearrangement of cyclic 2-thioaryloxyenones to annelated dihydrothiophenes and subsequent desulfurization give 3-arylcycloalkanones in high overall yield.

Sir: Introduction of an aryl substituent at a carbon atom β to a carbonyl group by conjugate addition of organocopper reagents to α,β-unsaturated carbonyl substrates has received considerable attention, *e.g.*, **1** → **2**.[1] Unfortunately, copper catalyzed reactions of arylmagnesium halides with α,β-unsaturated ketones usually give mixtures of 1,2- and 1,4-addition products. Conjugate addition may be more effectively performed by use of stoichiometric organocopper reagents prepared from an aryllithium and cuprous iodide;



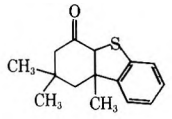
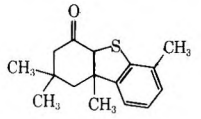
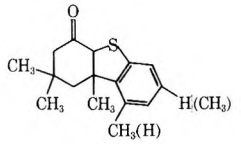
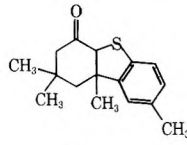
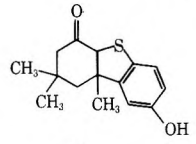
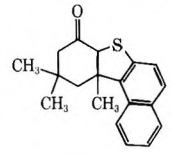
1 **2**

however, the required aryllithium may not always be obtainable. Furthermore, a two- or threefold excess of organocopper reagent is normally required for satisfactory conjugate addition and significant quantities of dimeric by-products may arise from coupling of the organocopper reagent.

In this paper, we report new methodology for the efficient and experimentally simple introduction of an aromatic nucleus β to a carbonyl group. The key step in the process involves the photocyclization–rearrangement of 2-thioaryloxyenones to dihydrothiophenes, *e.g.*, **3** → **5**.

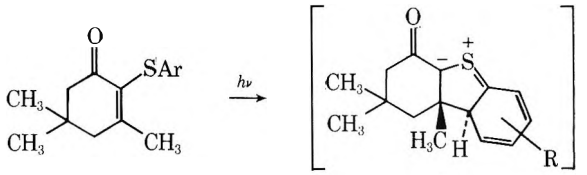
Cyclic 2-thioaryloxyenones **3** were prepared[2] in 92–98% yields by the potassium hydroxide catalyzed reaction of 1 equiv of aryl mercaptan with 2,3-epoxy-3,5,5-trimethylcyclohexanone.[3] Pyrex-filtered irradiation of **3** in benzene–methanol solution (3:1) in a conventional preparative photoreactor gave dihydrothiophenes **5** in excellent yield, Table I. This process presumably occurs by conrotatory photocyclization[4] in the excited state of **3** to give the intermediate thiocarbonyl ylide **4**, which suffers 1,4-hydrogen migration to give dihydrothiophene **5**.[5]

Table I
Photocyclization of 2-Thioaryloxyenones 3 to Dihydrothiophenes 5 and Desulfurization to 3-Arylcyclohexanones 2

2-Thioaryloxyenone	Dihydrothiophene 5 formed	% yield of 5[a]	% yield of 2[a]
3a		91	85
3b		88	87
3c		92[b]	
3d		84	86[c]
3e		83	83
3f		89	50

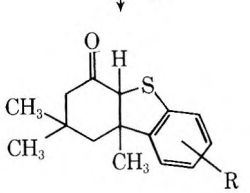
[a] Represents isolated yield of distilled or crystallized product. [b] Ratio of isomers is 70:30. [c] Product identical with that obtained by desulfurization of **5b**.

The conversion **3** → **5** in all cases examined except **3c** is completely regioselective and is applicable to large-scale



3a, Ar = phenyl
b, Ar = *o*-tolyl
c, Ar = *m*-tolyl
d, Ar = *p*-tolyl
e, Ar = *p*-hydroxyphenyl
f, Ar = 2-naphthyl

4



5

synthesis. The following procedure for preparation of **5a** is representative. A solution of **3a** (70.4 g) in benzene (1500 ml) and methanol (500 ml) was placed in a photoreactor fitted with a water-cooled immersion well containing a 450-W high-pressure mercury arc lamp. Dry argon was

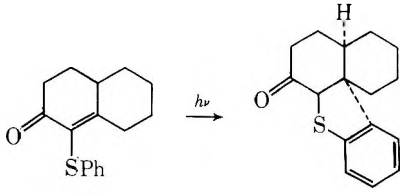
passed into the solution for 30 min prior to and during irradiation, and, after 20 hr, <0.5% **3a** was present in the nearly colorless reaction mixture (vpc analysis). Evaporation of solvent and crystallization from ether–petroleum ether gave **5a** (63.7 g, mp 80–82°).

Conversions of **5** to substituted 3-arylcyclohexanones **2** were best accomplished by desulfurization with freshly prepared Raney nickel in refluxing ethanol solution. While partial to complete hydrogenation of the carbonyl group in **5** accompanied desulfurization, treatment of the crude desulfurization product with Jones reagent gave ketone **2** in good overall yield, Table I.

No reduction of the aromatic ring occurred in **5a–e**; however, desulfurization of **5f** with Raney nickel or nickel boride[6] resulted in extensive reduction of the naphthalene ring. Refluxing the desulfurized ketone with excess dichlorodicyanobenzoquinone in benzene solution gave 3-(α-naphthyl)-3,5,5-trimethylcyclohexanone (**2f**) in moderate yield.

An advantage of photoarylation is demonstrated by the conversion of phenol **3e** to **2e** in 70% overall yield. This result is interesting because conjugate addition of organocopper reagents derived from *m*-bromophenol has not been successful.[7]

The stereochemical control possible with photoarylation is exceptionally high as demonstrated by conversion of 2-thiophenoxyoctalone **6** to dihydrothiophene **7**. Pyrex-filtered irradiation of **6** in benzene–methanol solution gave a single dihydrothiophene **7** (nmr, tlc, and vpc analysis) isolated as an oil in >95% yield. When desulfurized, **7** gave only *cis*-9-phenyldecalone-2 in high yield, which was identified by comparison with the product previously characterized from addition of lithiumdiphenylcuprate to $\Delta^{1(9)}$-octalone-2.[8] Exclusive formation of *cis*-decalone **7** in the photocyclization of **6** may be the result of preferential cyclization from the least hindered face of the enone system in **6.** This hypothesis is being tested in other fused-ring systems.



6 **7**

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References and Notes

(1) G. H. Posner, *Org. React.* **19**, 1 (1972).
(2) A. G. Schultz and D. S. Kashdan, *J. Org. Chem.*, **38**, 3814 (1973).
(3) E. I. Wasson and H. O. House, *Org. Syn.*, **37**, 58 (1957).
(4) A. G. Schultz and M. B. DeTar, *J. Amer. Chem. Soc.*, **96**, 296 (1974).
(5) Stereochemistry at the ring junction in **5** has not been established.
(6) W. E. Truce and F. M. Perry, *J. Org. Chem.*, **30**, 1316 (1965).
(7) For example, see N. Finch, L. Blanchard, R. T. Puckett, and L. H. Werner, *J. Org. Chem.*, **39**, 1118 (1974).
(8) S. M. McElvain and D. C. Remy, *J. Amer. Chem. Soc.*, **82**, 3960 (1960).

Department of Chemistry **Arthur G. Schultz**
Cornell University
Ithaca, New York 14850

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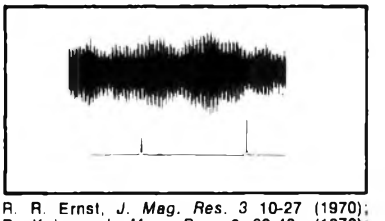

R. R. Ernst, *J. Mag. Res. 3* 10-27 (1970); R. Kaiser, *J. Mag. Res. 3* 28-40, (1970); J. Cooper and R. Addleman, 13th Experimental Nmr Conference (1972); E. Lippmaa, private communication.

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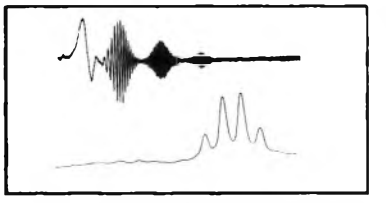

J. Dadok and R. F. Sprecher, 13th and 14th Experimental Nmr Conferences (1972, 1973); E. Becker, paper in press.

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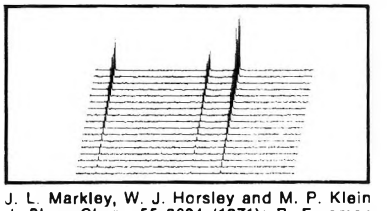

J. L. Markley, W. J. Horsley and M. P. Klein *J. Phys. Chem. 55* 3604 (1971); R. Freeman and H. D. W. Hill, *ibid. 54* April (1971); G. G. McDonald and J. S. Leigh, Jr., *J. Mag. Res.* 9 358 (1973).

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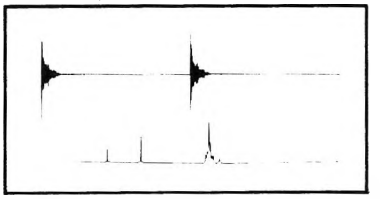

J. Schaeffer and E. O. Stejskal, 15th Experimental Nmr Conference (1974), and *J. Mag. Res.* March (1974) (in press). J. D. Ellett, et al. *Adv. Mag. Res.* 5 117 (1971)

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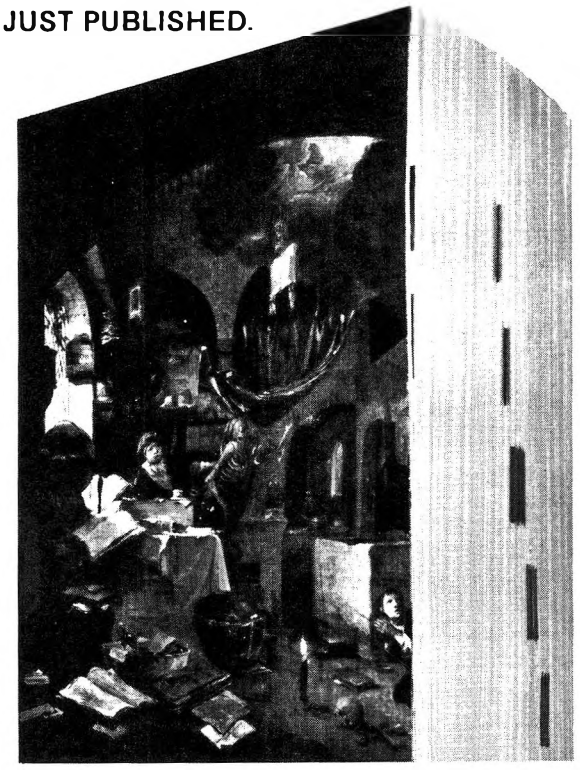

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