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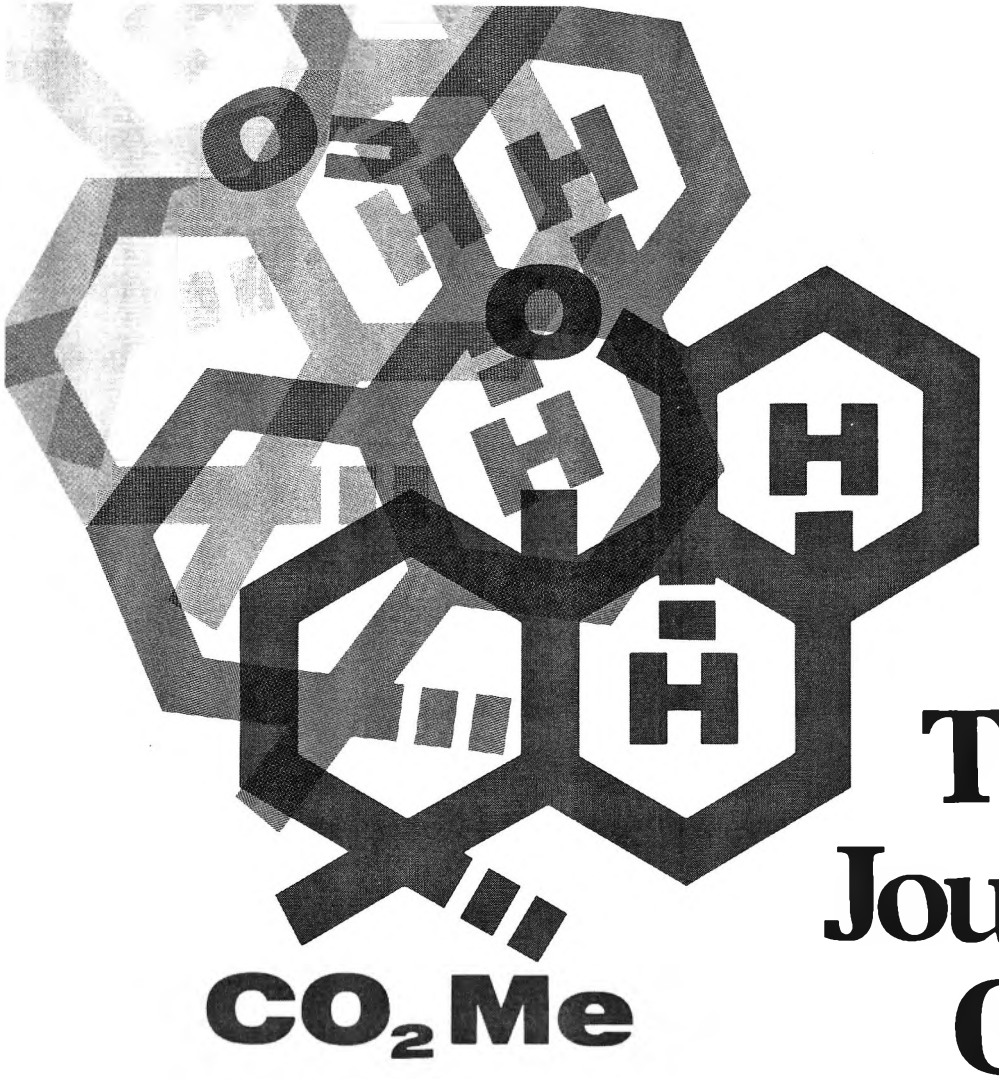

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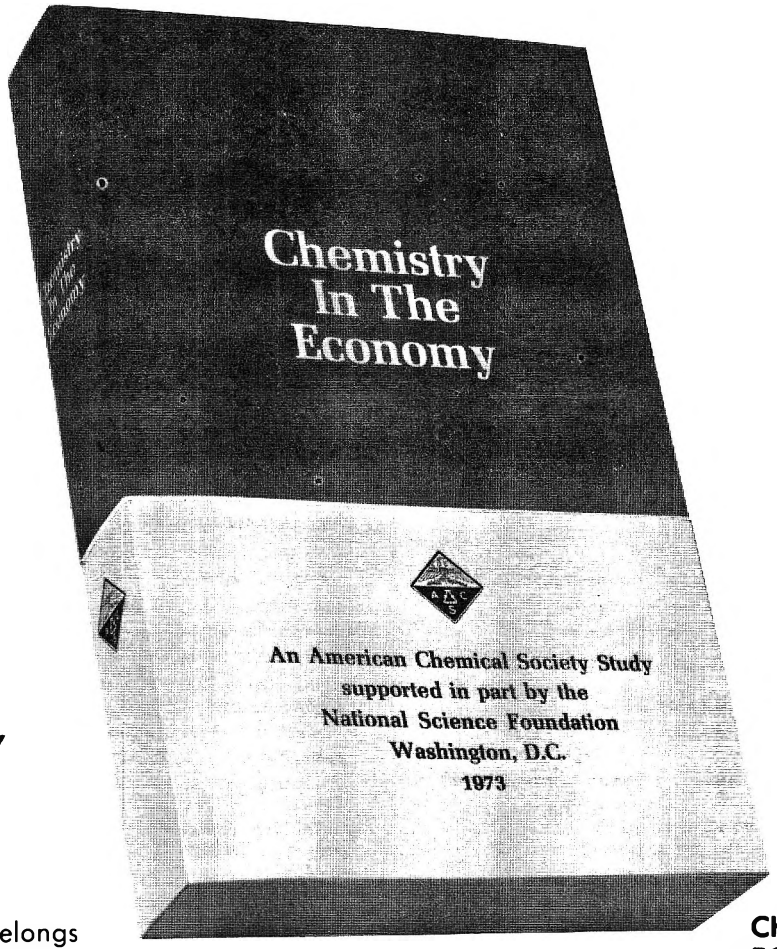

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Cycloaddition Reactions of Diarylthiirene 1,1-Dioxides with Enamines[1]

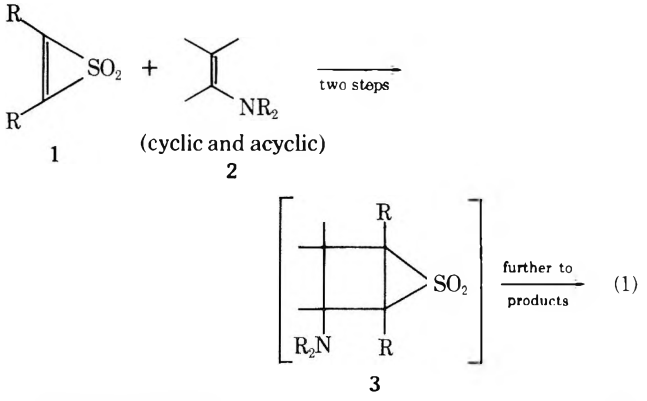
Melvin H. Rosen* and Georgina Bonet

Research Department, Pharmaceutical Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901

Received June 19, 1974

Reaction of 2,3-diphenylthiirene 1,1-dioxide (**5**) with enamines provided novel acyclic and cyclic systems. Products of carbon–carbon and carbon–sulfur bond cleavage in the intermediate episulfone **3** are described (eq 1). In some instances, medium- and large-sized sulfur-containing heterocycles are obtained in good yield. Other cases provided thiophene 1,1-dioxides which undergo a unique disproportionation reaction. Some of the medium-sized rings were heat labile and underwent transannular reactions on purification. Nuclear magnetic resonance decoupling experiments and employment of nmr complexing agents for the structural determination of these materials are described. Mechanistic interpretations are provided for all the results. The reaction is thought to be a thermal [2 + 2] cycloaddition with formation of **3** in a stepwise fashion. Subsequent scission of the cyclobutane portion of **3** could occur by a $[{}_{\delta}2_s + {}_{\delta}2_a]$ or stepwise process using the nonbonded pair of electrons of nitrogen. Products of loss of sulfur dioxide are more prevalent when **5** was substituted with a chloro group (**42**). Diarylthiirene 1,1-dioxides appear to have less conjugative stabilization than **4** and lack any aromatic character.

Knowledge of the synthesis and chemistry of thiirene 1,1-dioxides **1**[2-5] and the cycloaddition of α,β-unsaturated sulfones with electron-rich olefins **2**[6,7] indicated that employment of **1** in place of these sulfones might afford facile incorporation of its components, thus providing a unique method for the synthesis of novel acyclic and cyclic systems. The transformation would test the extent of nonbenzenoid aromatic character or the conjugative stabilization offered by the SO_2 group of **1** and would indicate the relative energetics involved with the cleavage of σ bonds within the expected intermediate **3** (eq 1).[8]



1 (cyclic and acyclic) **2**

(1)

3

Diphenylcyclopropenone (**4**) and **1** have been compared with respect to their reaction with base and it was found that **1** reacted approximately 5000 times faster than **4**; marked conjugative stabilization of **4** and slight conjugative stabilization of **1** were cited as the apparant explanation.[9] More recently, the reaction of enamines with **4** has received different interpretations[10] from the previously published results;[11] the present investigation compares those findings with these utilizing **1**.

Another goal was to demonstrate the synthetic potential for the reaction of **1** and **2** which could prove to be just as dramatic as realized in the treatment of the latter with dimethylacetylene dicarboxylate.[12-14] It would provide with cyclic **2** a facile entry into medium-sized ring sulfur containing heterocycles and thus would join the other methods described for the synthesis of analogous heterocyclic systems.[10f,15]

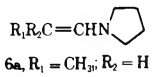
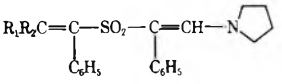
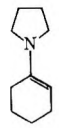
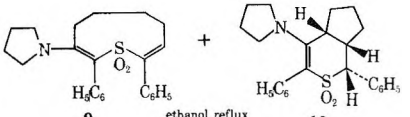
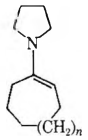
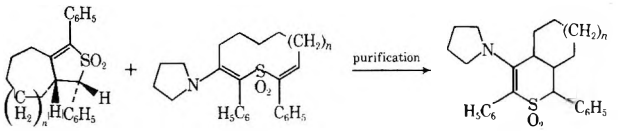
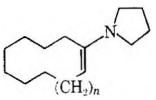
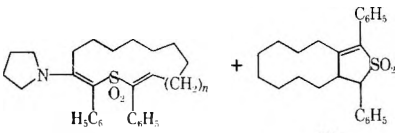
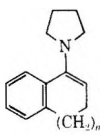
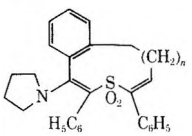
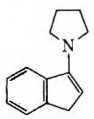
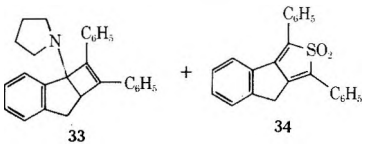
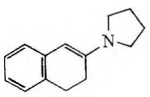
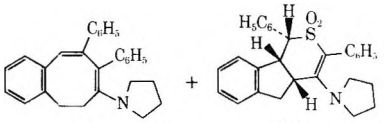
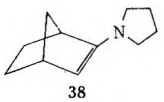
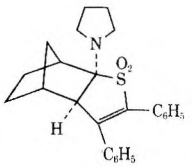
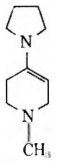
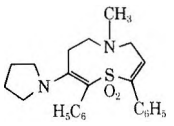
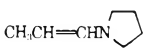
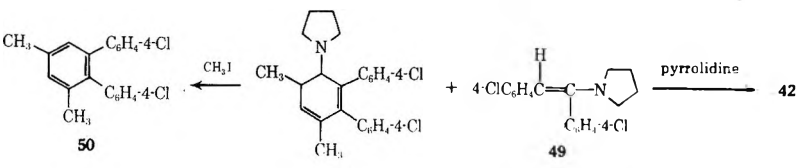
Results

An exothermic reaction between 2,3-diphenylthiirene 1,1-dioxide (**5**) and 1-(1-propenyl)pyrrolidine (**6a**) afforded vinylogous sulfonamide **7a** (Table I, eq a). The same transformation when controlled by intermittent cooling at 20° gave no physical evidence for an intermediate and the same product was obtained. Enamine **6b** and **6c** and **5** required external heating for transformation to **7b** and **7c**, respectively (Table I, eq a). The acyclic products were characterized unambiguously on the basis of spectral data and on comparisons with similar materials from the literature.[16] When enamine **6b** was modified from pyrrolidino to its piperidino, morpholino, and dimethylamino analogs, the usual decrease in enamine reactivity was observed[17] and no vinylogous sulfonamides were observed. Prolonged refluxing of reactants in benzene yielded diphenylacetylene, the sulfur dioxide extrusion product of **5**.

The reaction of **5** and 1-(1-cyclohexen-1-yl)pyrrolidine (**8**) was spontaneous on mixing in benzene and afforded a substance with a found empirical formula for a 1:1 adduct, $C_{24}H_{27}NO_2S$. Thin-layer chromatography indicated the presence of two components (*ca.* 80:20). The material was characterized before recrystallization since all suitable solvents of purification yielded a pure sample of the minor component. This new substance had the same empirical formula but possessed different physical and spectral properties. The major product has been assigned as nine-membered ring **9** and its isomer obtained on recrystallization as vinylogous sulfonamide **10** (Table I, eq b).

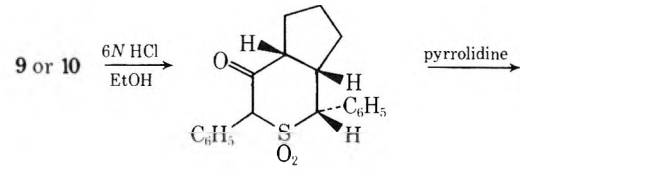
The structural assignment for **9** followed from its characteristic infrared absorption at 1520 cm^{-1} and its ultraviolet

Table I
Reactions of 2,3-Diphenyl (5) and 2,3-Bis(4-chlorophenyl)thiirene 1,1-Dioxide (42)

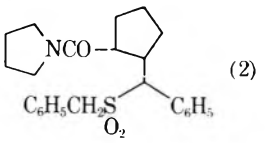
Enamine	Products	
 **6a**, $R_1 = CH_3$; $R_2 = H$ **b**, $R_1 = R_2 = CH_3$ **c**, $R_1 = C_6H_5$; $R_2 = H$	 **7a–c** **43b**[b]	(a)
 **8**	 **9** **44**[a,b] ethanol, reflux **10** **45**[b,c]	(b)
 **13**, $n = 1$ **14**, $n = 2$	 **15**, $n = 1$ **16**, $n = 2$ **17**,[a] $n = 1$ **18**,[a] $n = 2$ purification **19**, $n = 1$ **20**, $n = 2$	(c)
 **21**, $n = 1$ **24**, $n = 2$ **25**, $n = 3$	 **22**,[a] $n = 1$ **26**,[a] $n = 2$ **27**,[a] $n = 3$ **23**	(d)
 **29**, $n = 1$ **30**, $n = 2$	 **28**, $n = 1$ **31**, $n = 2$ **46**[b], $n = 1$	(e)
 **32**	 **33** **34**	(f)
 **35**	 **36** **47**[b] **37**	(g)
 **38**	 **39**	(h)
 **40**	 **41**[c]	(i)
 **6a**	 **50** **48** **49** **42**	(j)

[a] One of three possible structural assignments. [b] 4-ClC_6H_4 in place of C_6H_5. [c] 4-ClC_6H_4 is in the equatorial position since the coupling constant for the two adjacent protons is 13-Hz diaxial interaction.

absorption at 326 mμ. Employment of deuterated Eu(fod)$_3$ in its nmr spectrum furnished indirect evidence for the presence of a vinyl proton (Experimental Section). The configuration of the double bonds is unknown although the cis–cis appears to be in a relative sense the isomer with the least amount of transannular nonbonded interactions on inspection of Dreiding models. Evidence for the structural assignment for **10** was derived from its infrared and ultraviolet absorptions of 1550 cm^{-1} and 294 mμ, respectively.[16] Decoupling of the nmr spectrum demonstrated that the α-sulfonyl and methine protons were coupled to each other. Both **9** and **10** hydrolyze to sulfone **11** which affords a ring cleavage product (**12**) on treatment with pyrrolidine (eq 2).[18]



11



12 (2)

The course of reaction changed dramatically when the ring size of the enamine was increased. Treatment of **5** with 1-(1-cyclohepten-1-yl)- and 1-(1-cycloocten-1-yl)pyrrolidine, **13** and **14**, respectively, afforded dihydrothiophene 1,1-dioxides **15** and **16** as major products. In addition, 10-membered ring **17** and 11-membered ring **18** were observed and vinylogous sulfonamides **19** and **20** were isolated on purification (Table I, eq c).

The infrared spectra of **17** and **18** with their characteristic absorptions at 1520–1530 cm^{-1} and those for **19** and **20** at 1555–1560 cm^{-1} compared well with those obtained with **9** and **10**. The major products **15** and **16** were established on the basis of their spectral properties and through an awareness of what happens in the analogous diphenylcyclopropenone case (see Discussion).

Employment of 1-(1-cyclodecen-1-yl)pyrrolidine (**21**) with **5** afforded a 50:50 mixture of 13-membered ring **22** (stable to purification) and bicyclic dihydrothiophene 1,1-dioxide **23** (Table I, eq d). This reaction seems to be the point at which the formation of the large ring begins to become the major product again, for utilization of enamine **24** and **25** afforded in good yield the 14-membered and 15-membered rings, **26** and **27**, respectively (Table I, eq d).

Only one product, nine-membered ring **28**, was obtained on treatment of **5** with 1-(3,4-dihydro-1-naphthyl)pyrrolidine (**29**) (Table I, eq e). The structure of **28** followed from its infrared and ultraviolet spectra which compared with those of the above large rings (1524 cm^{-1} and 314 mμ, respectively). Nuclear magnetic resonance decoupling experiments and employment of deuterated Eu(fod)$_3$ provided the best evidence for the presence of the vinyl proton (Experimental Section). Assignment of all cis double bonds was based on the assumption that a trans double bond would yield a very strained system. The homologous enamine **30** afforded a ten-membered ring (**31**) (Table I, eq e). No dihydrothiophene 1,1-dioxide corresponding to **15** was isolated.

Reducing the ring size of **29**, that is, employment of 1-inden-3-ylpyrrolidine (**32**), gave a unique result. Instead of the expected eight-membered ring, olefin **33** and thiophene 1,1-dioxide **34** were isolated (Table I, eq f). The structures of these materials were established on the basis of their spectral properties (Experimental Section) and on mechanistic interpretation considered later (see Discussion).

A novel product was obtained when 1-(3,4-dihydro-2-naphthyl)pyrrolidine (**35**) was treated with **5**; dienamine **36** was isolated as the major and vinylogous sulfonamide **37** as the minor product (Table I, eq g). Decoupling of the nmr spectrum of **37** established the position of all of its protons (Experimental Section). The infrared and ultraviolet spectra for **36** when compared with similar materials in the literature[19] provided particularly striking evidence for its structural assignment (Experimental Section).

The course of reaction again changed when 1-(bicyclo[2.2.1]hept-2-en-2-yl)pyrrolidine (**38**) was employed; the sole isolated product was aminosulfone **39** (Table I, eq h). Evidence for the structure of **39** was established on the basis of its analytical spectra and mechanistic considerations to be discussed later. Although exo and endo ring fusion are both possible, **39** was assigned as the indicated exo fused ring according to literature precedence.[20] Direct proof for such an assignment would follow from the singlet nature of the endo hydrogen in the nmr spectrum since it would not be expected to couple with the bridgehead hydrogen. However, the region of the spectrum where this hydrogen would appear is masked by the rest of the hydrogens of the molecule.

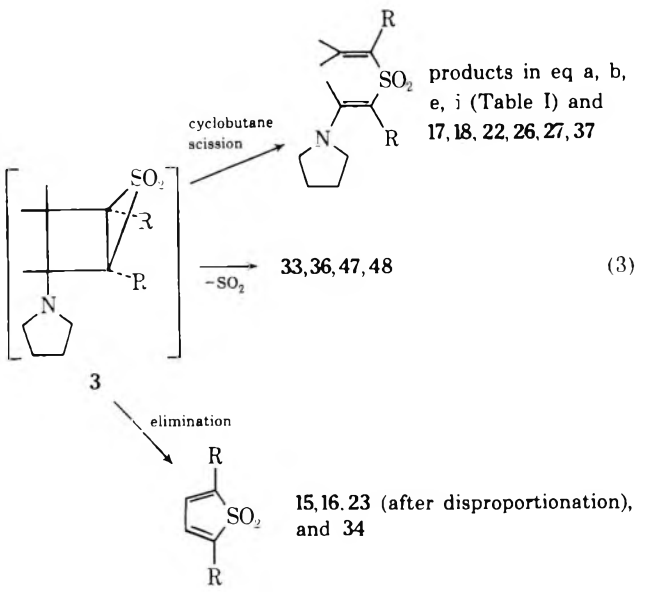
The synthetic value of this transformation is further emphasized by the employment of heterocyclic enamine **40** whereupon nine-membered ring **41** was obtained (Table I, eq i).

The effect of aromatic substitution in the thiirene 1,1-dioxide was investigated to see if the course of reaction would change. Synthesis of 2,3-bis(4-chlorophenyl)thirene 1,1-dioxide (**42**) was achieved in the usual manner[2] and reactions with several of the above enamines gave the analogous chloro-substituted products (Table I). One unique difference was the sole formation of **47** in twice the yield on comparison with the preparation of **36** (Table I, eq g). Another was the isolation of **48** and **49** on utilization of enamine **6a**; no product corresponding to **7a** was observed (Table I, eq i). Evidence for **48** lies in its analytical spectra and its degradation to a fully aromatic system, terphenyl **50**, on treatment with methyl iodide. Enamine **49** is an artifact since independently **42** yields the same material with pyrrolidine (Table I, eq j).

Discussion

The reaction of an enamine with a thiirene 1,1-dioxide can be considered as a thermal [2 + 2] cycloaddition which, according to orbital symmetry theory, is not a concerted process.[21] The transformation is represented in sequence 1 and intermediate **3** accounts directly or indirectly for all of the observed products, except for **39** (eq 3).

The transformation can be interpreted in another way. Participation of the nonbonded lone pair of electrons of the enamine nitrogen allows for a concerted [4n + 2] cycloaddition.[21] The first step in the mechanism is postulated as attack by the enamine on nitrogen[22] at the sulfonyl group of **1**[23] with subsequent addition to the β carbon of the vinylammonium ion; zwitterion **51** would result. This intermediate is similar to the one invoked for the corresponding reaction with diphenylcyclopropenone.[10] Bond reorganization could then afford all the described products (including **39**) (eq 4). However, such an interpretation seems unnecessary even though it accounts for **39** since this material could arise from an initial Michael addition of **38** and **5** (Table I, eq h) with subsequent bond reorganizations as shown with zwitterionic intermediates **52** and **53** (eq 4). In



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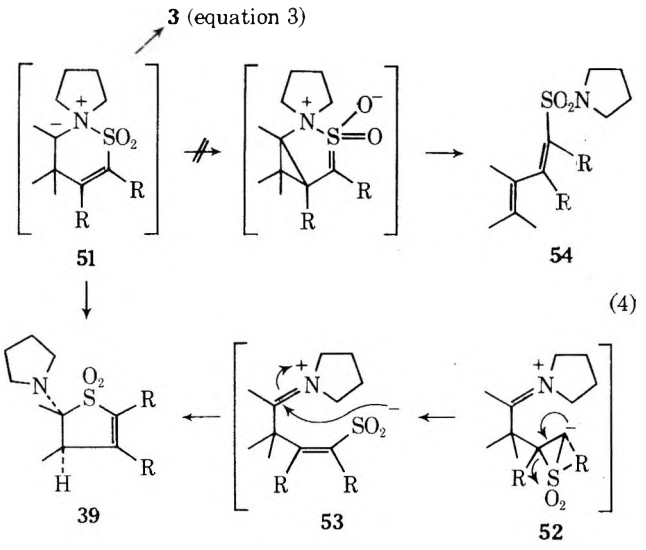


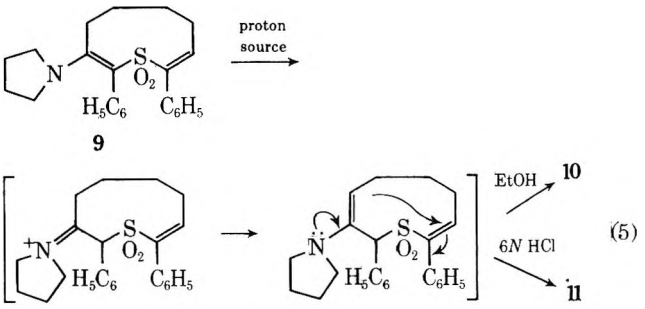
(4)

addition, no products were observed related to **54**,[24] one of the major structural types found in the analogous diphenylcyclopropenone case.[10]

Upon inspection of the results, loss of pyrrolidine and cyclobutane ring scission are processes where the C–C bond of the thiirane 1,1-dioxide part of **3** is cleaved. This bond has been shown through theoretical and experimental studies to be the weakest one.[8] Only **33** and **48** (as shown below) can be explained by a concerted extrusion of sulfur dioxide.[21,25] The driving force for relief of strain in the cyclobutane portion could account for the rarity of this pathway.

The concerted scission of a cyclobutane is a $[_{\delta}2_s + _{\delta}2_a]$ process which would yield the cis–cis structure,[21] but in the case of **3**, participation of the nonbonded pair of electrons of nitrogen after initial cleavage of the episulfone portion could account for the result.[8] In addition, it is unwise to assign the geometry of a molecule on the basis of Woodward–Hoffmann predictions since the steric interactions in the kinetic product might cause inversions to the more stable thermodynamic one. With these restrictions in mind, inspection of Dreiding models for materials like **9** predicts the cis–cis conformer to be favored and the best one to account for the facile transannular reaction encountered on purification (Table I, eq b) or acidic hydrolysis (eq 2). The possible mechanism for this is shown in eq 5.

Loss of pyrrolidine from **3** results in the formation of a thiophene 1,1-dioxide which in the transformation with **32**

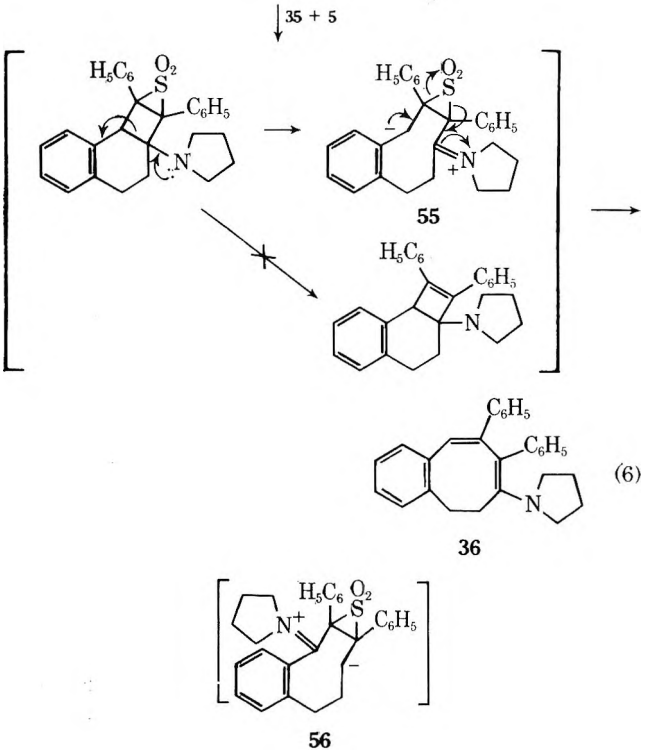


(5)

(Table I, eq f) was isolated (**34**). In the other instances (Table I, eq c and d) a disproportionation reaction would account for the products. Such an oxidation–reduction reaction is well documented in the enamine literature[26] and has been observed in analogous cyclopropenone investigations.[11]

Apparently the transannular nonbonded interactions for an eight-membered ring are severe ones, since employment of enamine **32** (Table I, eq f) afforded products of other pathways. Cyclobutene **33** showed no tendency to undergo a concerted conrotatory ring opening to a cycloheptatriene.[21] Such an event would yield an undesired trans double bond. The material was not heated at a sufficient temperature (*i.e.*, 400°) to undergo the disrotatory process observed for an analogous material in the literature.[27]

It is unlikely that **36** and **47** are derived from initial loss of sulfur dioxide based on the above discussion, for such an occurrence followed by a concerted opening of the derived cyclobutene would afford a trans double bond in a cyclooctatriene. The temperature of the transformation seems too low to allow the corresponding disrotatory mode of ring opening (eq 6). If the lone pair of electrons on nitrogen aids the opening, then such a process should also apply for the former case (enamine **32**). The driving force for this transformation (Table I, eq g) is apparently the formation of a benzylic carbanion (intermediate **55**) which could undergo bond neutralization as shown (eq 6). The same stabilization is not present in the corresponding intermediate **56** from employment of enamine **29** (or **32**). In addition, **28**, and **37** are stable to extended reflux in benzene.



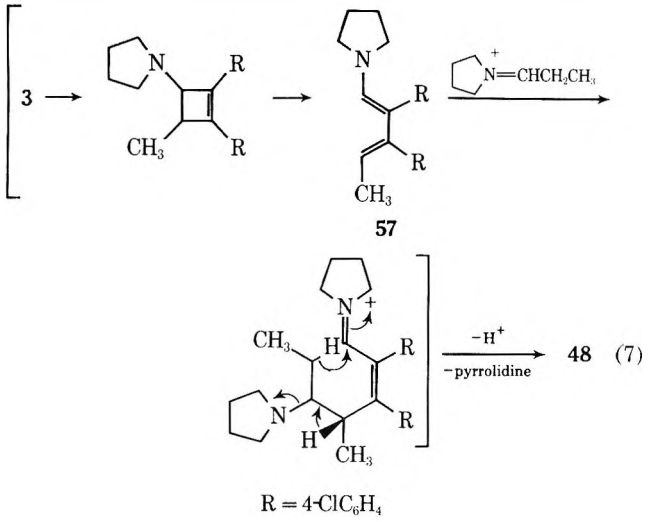
(6)

Table II
Experimental Conditions for the Reactions of 2,3-Diphenylthiirene 1,1-Dioxide (5)

Product(s)	5 (g, mol)	Enamine (g, mol)	Benzene, ml	Temp, °C	Time, min
7a	3.0, 0.012	**6a**[e] (2.0, 0.018)	30	80[b]	15
7b	5.0, 0.02	**6b**[e] (3.5, 0.028)	15	80[b]	120
7c	3.0, 0.012	**6c**[f] (3.0, 0.017)	15	65[a]	120
9, 10[d]	17.0, 0.07	**8**[g] (12.0, 0.08)	300	40[b]	15
15, 17, 19[d]	2.3, 0.01	**13**[g] (1.8, 0.01)	30	40[b]	10
16, 18, 20[d]	6.0, 0.025	**14**[g] (4.5, 0.025)	60	60[b]	10
22, 23	3.5, 0.015	**21** (3.3, 0.016)	30	30[b]–65[a]	120
26	3.5, 0.015	**24** (3.5, 0.016)	30	30[b]–65[a]	120
27	3.0, 0.012	**25**[h] (3.2, 0.014)	30	30[b]–60[a]	120
28	6.0, 0.025	**29**[i] (5.5, 0.028)	45	80[a]	90
31	3.0, 0.012	**30**[j] (3.0, 0.014)	30	60[a]	120
33, 34	5.0, 0.02	**32**[k] (4.0, 0.022)	30	60[b]	5
36, 37	4.0, 0.017	**35**[22] (3.5, 0.017)	30	70[a]	180
39	6.0, 0.025	**38**[l] (4.8, 0.003)	50	65[b]–70[a]	120
41	6.0, 0.025	**40**[m] (4.2, 0.025)	30	15[c]	120

[a] Reaction mixture was externally heated. [b] Reaction mixture was exothermic to this temperature. [c] Reaction mixture was externally cooled. [d] Material obtained from purification of one of the other products from the reaction. In each case, see specific experiment. [e] G. Opitz, H. Hellmann, and H. W. Schubert, *Justus Liebigs Ann. Chem.*, **623**, 112 (1959). [f] J. N. Wells and F. S. Abbott, *J. Med. Chem.*, **9**, 489 (1966). [g] M. E. Kuehne, *J. Amer. Chem. Soc.*, **81**, 5400 (1959). [h] K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963). [i] G. Bianchi and E. Frati, *Gazz. Chim. Ital.*, **96**, 559 (1966). [j] L. H. Hellberg, R. J. Milligan, and R. N. Wilke, *J. Chem. Soc. C*, 35 (1970). [k] E. D. Bergmann and E. Hoffmann, *J. Org. Chem.*, **26**, 3555 (1961). [l] J. F. Stephen and E. Marcus, *J. Org. Chem.*, **34**, 2535 (1969). [m] S. Donishefsky and R. Cavanaugh, *J. Org. Chem.* **33**, 2959 (1968).

The electronic influences operative in 2,3-bis(4-chlorophenyl)thiirene 1,1-dioxide (**42**) allow the loss of sulfur dioxide to compete to a greater extent.[28] Not only is the yield of **47** much greater, the products obtained with **6a** (Table I, eq j) lack the sulfonyl group. Formation of **48** is best envisioned as a loss of sulfur dioxide from intermediate **3** and ring opening of the intermediate cyclobutene. The intermediate butadiene **57** could add in a typical enamine fashion to the protonated form of **6a** with subsequent loss of a proton and pyrrolidine from that intermediate to afford **48** (eq 7).[29] The materials **48** and **49** are not formed



(7)

by reaction of enamine **6a** or pyrrolidine with bis(4-chlorophenyl)acetylene for such transformations were shown to afford starting materials.

From comparisons of Tables II and III (Experimental Section) with the data furnished in ref 10 and 11,[30] it becomes apparent that the reaction of enamines with diarylthiirene 1,1-dioxides (**1**) is qualitatively a much faster one than with diphenylcyclopropenone. Perhaps this is further evidence for the slight conjugative stabilization and lack of aromatic character of **1**.[4,8c]

The synthetic utility of this transformation for 9-, 10- (in the case of **31**), 14-, and 15-membered sulfur-containing heterocycles has been demonstrated. In the other ring cases, the course of reaction is dependent on competing steric and electronic factors.

Experimental Section

General Comments. Melting points were determined on a Thomas Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 21 or 521 grating spectrophotometer and performed in Nujol (abbreviation: en, enamine); ultraviolet spectra were recorded on a Cary 14 and performed in methanol. The nuclear magnetic resonance spectra were determined in deuterated chloroform unless otherwise stated and performed on a Varian A-60, XL-100, or HA-100 instrument. Absorptions are quoted in δ values against tetramethylsilane as internal standard (abbreviations: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; cp, complex pattern; p, proton, Ar, aryl; pyrr, pyrrolidino group). Mass spectra were obtained on an AEI MS-902 spectrometer (70 cV). Elemental analyses were done on a Perkin-Elmer 240.

Starting Materials. Most of the starting materials were prepared according to the literature (see Table II for references). The following are unknown (except for **42**) and synthesized as indicated.

1-(1-Cyclodecen-1-yl)pyrrolidine (21) was obtained in 49.0% yield (3.3 g) by refluxing a solution of 5.0 g (0.03 mol) of cyclodecanone, 6.0 g (0.08 mol) of pyrrolidine, 0.2 g of *p*-toluenesulfonic acid, and 75 ml of toluene for 24 hr using a Dean-Stark trap for water separation. Concentration of the solution *in vacuo* and distillation afforded **21**: bp 90° (0.25 mm); nmr δ (60 MHz) 4.05 (t, 1, J = 10 Hz, vinyl p).

1-(1-Cycloundecen-1-yl)pyrrolidine (24) was obtained in 53.0% yield (3.5 g) by refluxing a solution of 5.0 g (0.03 mol) of cycloundecanone, 6.0 g (0.08 mol) of pyrrolidine, 0.3 g of *p*-toluenesulfonic acid, and 75 ml of toluene for 48 hr as above: bp 99–100° (0.25 mm); nmr δ (60 MHz) 3.95 (t, 1, J = 10 Hz, vinyl p).

α,α'-Sulfonylbis(α-bromo-4-chloro)toluene was prepared by method B in ref 5: mp 195–200° (47.8% yield).

Anal. Calcd for $C_{14}H_{10}Br_2Cl_2O_2S$: C, 35.47; H, 2.13. Found: C, 35.03; H, 2.57.

2,3-Bis(4-chlorophenyl)thiirene 1,1-Dioxide (42). A stirred solution of 312 g (0.66 mol) of the above material in 1800 ml of toluene was treated at the initial reflux temperature but with the heat source removed with 480 ml of triethylamine in 5 min. The mixture was cooled immediately in an ice bath. The solid was filtered and stirred with 2000 ml of water, filtered, and the operation repeated with 2000 ml of aqueous hydrochloric acid solution (3 N). The solid was suspended in ethanol, filtered, and air dried to afford **42** in 16.6% yield (51.8 g): mp 174–177° (same mp as the derived acetylene);[31] ir 1590 (double bond), 1260, 1155, and 1090

Table III
Experimental Conditions for the Reactions of 2,3-Bis(4-chlorophenyl)thiirene 1,1-Dioxide (42)

Product(s)	40; g, mol	Enamine (g, mol)	Benzene, ml	Temp, °C	Time, min
43[b]	3.0, 0.01	**6b** (2.5, 0.02)	30	70[a]	120
44, 45[c]	15.3, 0.05	**8** (8.0, 0.05)	150	35[b]–50[a]	120
46	5.0, 0.016	**29** (3.5, 0.017)	30	65[a]	180
47	6.75, 0.022	**35** (4.0, 0.02)	30	70[a]	180
48, 49	3.0, 0.01	**6a** (2.2, 0.02)	30	30[b]–65[a]	120

[a] Reaction mixture was externally heated. [b] Reaction mixture was exothermic to this temperature. [c] This material was obtained from purification of **42** (see experimental procedure).

cm^{-1} (all SO_2); uv max 226 (20,200), 234 sh (16,600), 271 sh (13,100), 288 (16,800), 306 (21,400), 318 (20,700), and 334 mμ (14,900); nmr δ (DMSO-d_6) (60 MHz) 7.50–8.00 (cp due to decomposition to the acetylene, Ar); mass spectra M^+ 311 (20 eV).

Anal. Calcd for $C_{14}H_8Cl_2O_2S$: C, 54.04; H, 2.59. Found: C, 53.80; H, 2.59.

The above toluene filtrate was concentrated to dryness *in vacuo* and the residue was stirred with water and filtered. The remaining solid was refluxed in 400 ml of benzene for 10 min and filtered hot. Cooling the benzene solution afforded 11.7 g of bis(4-chlorophenyl)acetylene, mp 174–177°.

General Procedure for the Reaction of Thiirene 1,1-Dioxides 5 and 42 with Enamines. Tables II and III describe the amounts of reactants, the experimental conditions, and the products of the reaction of **5** and **42** with the designated enamines. Unless otherwise stated, the following procedure is typical of that employed for these materials. A stirred mixture of **5** or **42** and two-thirds the quoted amount of anhydrous benzene was treated dropwise under nitrogen with a solution of the enamine in the remaining specified benzene. In some cases the reaction was exothermic (footnote *b* in Tables II and III) and was maintained at the indicated temperature for the specified time by regulating the addition of the benzene–enamine solution. In the instances where the reaction was not exothermic (footnote *a* in Tables II and III), the addition of the benzene–enamine solution was very rapid and the reaction mixture was externally heated at the reported temperature and time specified. In all cases, the reaction was allowed to cool to ambient temperature and left overnight. Some of the products crystallized directly from the reaction mixture while others were obtained upon concentration of the mixture *in vacuo* and trituration with ethanol–ether.

1-[2-Phenyl-2-[(1-phenyl-1-propenyl)sulfonyl]ethenyl]pyrrolidine (7a) was isolated in 20.6% yield (0.9 g); mp 161–163°. Analytical sample prepared from ethanol showed: mp 165–166.5°; ir 1610 (en), 1282 and 1120 (both SO_2), strong bands at 768, 705, and 650 cm^{-1}; uv max 286 mμ (17,000); nmr δ (60 MHz) 1.40–1.80 [cp with superimposed d (approximately 1.53, J = 7.0 Hz), 7, CH_2, pyrr and CH_3CH=], 2.63–3.05 (cp, 4, CH_2NCH_2), 6.64 (q, J = 7.0 Hz, 1, CH_3CH=), 7.07 (br s, 1, >NCH=), and 7.24 and 7.30 (s, 10, Ar); mass M^+ 353.

Anal. Calcd for $C_{21}H_{23}NO_2S$: C, 71.35; H, 6.56; N, 3.96. Found: C, 71.09; H, 6.57; N, 3.92.

1-[2-[(2-Methyl-1-phenyl-1-propenyl)sulfonyl]-2-phenylethenyl]pyrrolidine (7b) was isolated in 31.3% yield (2.3 g), mp 120–122°. Analytical sample obtained from ethanol showed: mp 121–122°; ir 1602 (en), 1287 and 1118 (both SO_2), strong bands at 700, 665, and 650 cm^{-1}; uv max 286 mμ (18,700); nmr δ (60 MHz) 1.40–1.92 (cp with two superimposed s at 1.48 and 1.85, 10, CH_2, pyrr and $(CH_3)_2C$=), 2.68–3.10 (cp, 4, CH_2NCH_2), and 6.84–7.50 (cp with superimposed s at 7.29, 11, vinyl and Ar); mass M^+ 367.

Anal. Calcd for $C_{22}H_{25}NO_2S$: C, 71.78; H, 6.85; N, 3.81. Found: C, 72.15; H, 6.73; N, 3.80.

1-[2-[(1,2-Diphenylethenyl)sulfonyl]-2-phenylethenyl]pyrrolidine (7c) was obtained in 73.8% yield (3.8 g), mp 142–145°. Analytical sample from ethanol showed: mp 150–151°; ir 1605 (en), 1280 and 1115 (both SO_2), medium to strong bands at 990, 945, 755, 697, 688, 650, and 662 cm^{-1}; uv max 256 (18,800) and 308 mμ (18,500); nmr δ (60 MHz) 1.45–1.78 and 2.65–3.00 (cp, 4 each, pyrr p), and 6.68–7.45 (m with two superimposed singlets at 7.00 and 7.32, 17, vinyl and Ar); mass M^+ 415.

Anal. Calcd for $C_{26}H_{25}NO_2S$: C, 75.15; H, 6.06; N, 3.37. Found: C, 74.90; H, 5.96; N, 3.42.

Formation of 9 and 10. Reaction of 1-(1-Cyclohexenyl)pyrrolidine (8) with 5. 2,9-Diphenyl-3-(1-pyrrolidinyl)-4,5,6,7-tetrahydrothionin 1,1-dioxide (9) was obtained by direct crystallization analytically pure after washing with ether in 86.5% yield 23.9 g), mp 135–137° dec (the melting point of **9** is lower and over a wider range if the temperature of the experiment is not carefully controlled at 70°; thin-layer analysis in these instances indicates the presence of **10**): ir 1520 (en), 1277 and 1124 (both SO_2), medium to strong bands at 1022, 932, 758, 704, 690, and 656 cm^{-1}; uv max 234 (16,900), 260 (11,400), and 326 mμ (8760); nmr δ (100 MHz) 1.40–1.90 (m, 12, CH_2 of nine-membered and pyrr rings), 2.70–3.20 (m, 4, CH_2NCH_2), and 6.90–7.60 (cp, 11, vinyl and Ar). The spectrum of this material as noted is very broad owing to the many signals concentrated over a small chemical-shift range. It was virtually impossible to identify any long range or the vicinal coupling of the vinyl proton. However, utilization of deuterated Eu(fod)$_3$ afforded complexation and a shift to lower field of the aromatic and the vinyl protons (dd), but temperature effects did not allow for accurate integration. This experiment is complimentary to the detailed description of the complexation in the spectrum for **28**. Mass spectrum was M^+ 393.

Anal. Calcd for $C_{24}H_{27}NO_2S$: C, 73.24; H, 6.92; N, 3.55. Found: C, 73.47; H, 6.81; N, 3.68.

1,4a,5,6,7,7a-Hexahydro-1,3-diphenyl-4-(1-pyrrolidinyl)cyclopenta[*c*]thiopyran 2,2-dioxide (10) was afforded by recrystallization of **9** (1.0 g) from ethanol in 45.0% yield (0.45 g): mp 243–244° dec; ir 1550 (en), 1270 and 1115 (both SO_2), medium to strong bands at 890 and 696 cm^{-1}; uv max 219 (20,000), 262 (11,000), and 294 mμ (8430); nmr δ (100 MHz) 1.50–1.80 (cp, 10, CH_2 of fused five-membered and pyrr rings), 2.80–3.30 (cp, 6, angular methines and CH_2NCH_2), 4.5 (d, 1, α-sulfonyl p, J = 6.00 Hz (equatorial–axial), 7.15–7.45 and 7.50–7.70 (two cp, 8 and 2, Ar); a decoupling experiment located the group coupled to the α-sulfonyl proton at 3.0 ppm; mass M^+ 393.

Anal. Calcd for $C_{24}H_{27}NO_2S$: C, 73.24; H, 6.92; N, 3.55. Found: C, 73.00; H, 6.97; N, 3.57.

Acidic Hydrolysis of 9 and 10 to 1,4a,5,6,7,7a-Hexahydro-1,3-diphenylcyclopenta[*c*]thiopyran-4(3*H*)-one 2,2-Dioxide (11). A stirred slurry of 2.7 g (0.0069 mol) of **9** and 25 ml of 95% ethanol was treated over 5 min with 6 ml of 6 *N* aqueous hydrochloric acid solution. A solution was obtained in 10 min and the stirred reaction mixture was heated at reflux for 2.5 hr and left at ambient temperature overnight. Filtration of the precipitate and washing of the solid with ether gave **11** in 98% yield (2.3 g), mp 235–237°. Analytical sample from ethyl acetate showed: mp 249–250°; ir 1727 (C=O), 1320, 1310, 1295, 1142, 1122, and 1082 cm^{-1} (all SO_2); uv max 219 (23,500) and 258 mμ (850); nmr δ (DMSO-d_6) (60 MHz) 1.17–2.8 (two multiplets, 6, methylene p), 3.30 (m, 2, methine p), 5.32 [d, J = 5.0 Hz (equatorial–axial), 1, $SO_2CHC_6H_5$], 5.98 (s, 1, $SO_2C(-C_6H_5)HCO$), and 7.40 (br s, 10, Ar); mass M^+ 340.

Anal. Calcd for $C_{20}H_{20}O_3S$: C, 70.55; H, 5.92. Found: C, 70.60; H, 5.90.

A stirred solution of 0.5 g (0.0013 mcl) of **10**, 5 ml of 95% ethanol, and 5 ml of saturated ethanolic hydrochloric acid solution was refluxed for 1.5 hr and left at ambient temperature overnight. Concentration of the reaction mixture and recrystallization of the resultant solid from ethanol gave **11** in 46.5% yield (0.2 g), mp 235–237°. The material possessed identical physical properties when compared with the above data.

Reaction of 11 and Pyrrolidine to 2-[α-(Benzylsulfonyl)benzyl]cyclopentanecarbonyl Piperidide (12). A mixture of 1.5 g (0.004 mol) of **11**, 2.0 g (0.03 mol) of pyrrolidine, and 150 ml of dry benzene was contained in a 300-ml round-bottomed flask topped by a 12-in. column containing glass helices and equipped with a Dean-Stark trap. The mixture was refluxed for 2 hr whereupon a solution was obtained and reflux was maintained overnight. Concentration *in vacuo* gave an 83.3% yield of **12** (1.5 g), mp 178–180°. An analytical sample was obtained from acetone: mp 183–184°; ir 1625 (amide), 1310, 1290, and 1125 (all SO_2), medium bands at 700 and 690 cm^{-1}; nmr δ (60 MHz) 1.25–2.10 (m, 10, CH_2 of the rings), 2.20–3.30 (two m, 6, CH_2NCH_2 and methines of

five-membered ring), 3.75–4.15 (cp with superimposed s at 3.84, 3, $CHSO_2CH_2$), and 7.27 and 7.37 (two s, 10, Ar); mass M^+ 411.

Anal. Calcd for $C_{24}H_{29}NO_3S$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.34; H, 7.07; N, 3.16.

Formation of 15, 17, and 19. Reaction of 1-(1-Cyclohepten-yl)pyrrolidine (13) with 5. 5,6,7,8-Tetrahydro-2,10-diphenyl-3-(1-pyrrolidinyl)-4*H*-thiecin 1,1-dioxide (17) was isolated by direct crystallization and obtained analytically pure after washing with ether in 5.0% yield (0.2 g): mp 121–123° dec; ir 1521 (en), 1267, 1240, 1134, 1106 (all SO_2), and medium peaks at 740 and 680 cm^{-1}; mass M^+ 407. (Attempts to obtain nmr and uv data in deuterated chloroform and methanol, respectively, afforded spectra characteristic of **19**. However, one experiment performed in a uv tube with acetonitrile as solvent gave a spectrum with a uv max of 327 mμ.) Only this experiment afforded pure **17**. In all other attempts, **17** was isolated along with **15** and attempted purification *via* chromatography on alumina or fractional crystallization gave **19**.

Anal. Calcd for $C_{25}H_{29}NO_2S$: C, 73.67; H, 7.17; N, 3.44. Found: C, 73.30; H, 7.05; N, 3.63.

Recrystallization of **17** from ethanol afforded **4a,5,6,7,8,8a-hexahydro-1,3-diphenyl-4-(1-pyrrolidinyl)-1*H*-2-benzothiopyran 2,2-dioxide (19)** in 45.0% yield, mp 259–260° dec; ir 1560 (en), 1268 and 1108 (both SO_2), medium to strong bands at 920, 730, and 698 cm^{-1}; uv max 219 (22,100), 262 (11,600), and 295 mμ (7360); mass M^+ 407. (Poor solubility in organic solvents prevented the determination of the 60-MHz nmr spectrum.)

Anal. Calcd for $C_{25}H_{29}NO_2S$: C, 73.67; H, 7.17; N, 3.44. Found: C, 73.39; H, 7.17; N, 3.47.

Diluting the filtrate from the isolation of **17** with ether and cooling overnight at 0° gave **3a,4,5,6,7,8-hexahydro-1,3-diphenyl-3*H*-cyclohepta[*c*]thiophene 2,2-dioxide (15)** in 74.0% yield (2.5 g). An analytical sample was obtained (ethanol): mp 125–127°; ir 1284 and 1120 (both SO_2), and strong bands at 752 and 690 cm^{-1}; uv max 240 mμ (9100) and end absorption; nmr δ (60 MHz) 1.00–2.80 (two m, 10, methylene p), 3.40 (m, 1, methine p), 4.60 (d, 1, α-sulfonyl p, J = 7.0 Hz, equatorial–axial coupling), and 7.38 and 7.45 (two s, 10, Ar); mass M^+ 338.

Anal. Calcd for $C_{21}H_{22}O_2S$: C, 74.52; H, 6.55; S, 9.48. Found: C, 74.36; H, 6.36; S, 9.35.

Formation of 16, 18, and 20. Reaction of 1-(1-Cyclooctenyl)pyrrolidine 14 with 5. 1,4,5,6,7,8,9,9a-Octahydro-1,3-diphenylcycloocta[*c*]thiophene 2,2-dioxide (16) was isolated in 82.8% yield (7.3 g), mp 144–146°. Analytical sample obtained from ethanol showed: mp 158–160° slight dec; ir 1295 and 1129 (both SO_2), and strong band at 695 cm^{-1}; uv max 240 mμ sh (8920) and end absorption; nmr δ (60 MHz) 1.17–2.75 (two m, 12, methylene p), 3.22 (m, 1, methine p), 4.62 [d, 1, α-sulfonyl p, J = 7.0 Hz (equatorial–axial)], and 7.46 (s, 10, Ar); mass M^+ 352.

Anal. Calcd for $C_{22}H_{24}O_2S$: C, 74.96; H, 6.86; S, 9.10. Found: C, 74.77; H, 6.73; S, 9.04.

Examination of the infrared spectrum of crude **16** (mp 144–146°) showed absorption at 1530 cm^{-1} for **2,11-diphenyl-3-(1-pyrrolidinyl)thiacycloundeca-2,10-diene 1,1-dioxide (18)**. Chromatography of residues from combined filtrates on 100 g of Woelm neutral alumina (activity 1) gave on elution with 1000 ml of petroleum ether (30–60°), 1000 ml of 50:50 petroleum ether–ethyl ether, and 500 ml of ethyl ether, 0.4 g of **16**, mp 132–135°. Further elution with 500 ml of ethyl ether gave 0.05 g of **1,4a,5,6,7,8,9,9a-octahydro-1,3-diphenyl-4-(1-pyrrolidinyl)cyclohepta[*c*]thiopyran 2,2-dioxide (20)**: mp 200–201°; ir 1555 (en), 1270 and 1115 (both SO_2), medium to strong bands at 868, 766, 700, and 670 cm^{-1}; uv max 215 sh (17,500), 256 (9110), and 295 mμ (7790); mass M^+ 421.

Anal. Calcd for $C_{26}H_{31}NO_2S$: mass spectrum molecular weight ion 421.208. Found: 421.208.

Formation of 22 and Evidence for 23. Reaction of 1-(1-Cyclodecenyl)pyrrolidine (21) with 5. The generalized procedure yielded 2.1 g of a brown solid, mp 86–100°; the thin layer indicated two major compounds; ir 1520 (en), 1280, and 1112 cm^{-1} (SO_2, most intense bands of spectrum); uv max 306 mμ (7170); uv min 272 mμ (4710); nmr δ same as spectrum reported below with a superimposed doublet at 4.65 (J = 7.0 Hz, 1, α-sulfonyl p) (*ca.* 25% of expected intensity). Recrystallization from the common organic solvents gave oils. Chromatography on Woelm neutral alumina (activity 1) afforded 0.7 g (9.3% yield) of a colorless material (elution with 75:25 hexane–ether, 1000 ml, and with 5:50 hexane–ether, 1000 ml), mp 145–147°. Analytical sample of **2,13-diphenyl-3-(1-pyrrolidinyl)thiacyclotrideca-2,12-diene 1,1-dioxide (22)** from acetonitrile had: mp 153–154°; ir 1535 (en), 1286 and 1117 (both SO_2), strong to medium bands at 938, 717, 698, 670, and 645 cm^{-1}; uv max 224 sh (14,900), 268 sh (6380), and 308 mμ (12,800); nmr δ (60 MHz) 1.30–2.30 (two m, 20, CH_2 of 13-membered and pyrr rings), 2.60–3.10 (m, 4, CH_2NCH_2), and 6.50–7.40 (cp, 11, vinyl and Ar); mass M^+ 449.

Anal. Calcd for $C_{28}H_{35}NO_2S$: C, 74.80; H, 7.85; N, 3.12. Found: C, 74.71; H, 7.95; N, 3.05.

Even though **23** was not isolated, the evidence described in the first part of this experiment is conclusive for its presence.

2,14-Diphenyl-3-(1-pyrrolidinyl)thiacyclotetradeca-2,13 diene 1,1-dioxide (26) was isolated in 59.6% yield (4.0 g), mp 144–145°. Analytical sample from acetonitrile had: mp 145–147°; ir 1522 (en), 1279 and 1120 (both SO_2), strong band at 697 cm^{-1}; uv max 224 sh (15,900) and 303 mμ (13,300); nmr δ (60 MHz) 1.25–2.20 (two m, 22, CH_2 of 14-membered and pyrr rings), 2.60–3.10 (m, 4, CH_2NCH_2), and 6.60–7.30 (cp, 11, vinyl and Ar); mass M^+ 463.

Anal. Calcd for $C_{29}H_{37}NO_2S$: C, 75.13; H, 8.05; N, 3.02. Found: C, 75.38; H, 7.95; N, 3.31.

2,15-Diphenyl-3-(1-pyrrolidinyl)thiacyclopentadeca-2,14-diene 1,1-dioxide (27) was obtained in 61.5% yield (3.5 g), mp 151–152°. Analytical sample prepared from acetonitrile had: mp 155–156°; ir 1525 (en), 1275 and 1117 (both SO_2), and strong band at 692 cm^{-1}; uv max 220 sh (16,600) and 301 mμ (10,900); nmr δ (60 MHz) 1.20–2.20 (two m, 24, CH_2 of 15-membered and pyrr rings), 2.60–3.00 (m, 4, CH_2NCH_2), and 6.80–7.50 (cp, 11, vinyl and Ar); mass M^+ 477.

Anal. Calcd for $C_{30}H_{39}NO_2S$: C, 75.43; H, 8.23; N, 2.93. Found: C, 75.80; H, 8.07; N, 2.56.

Combined residues from filtrates chromatographed on 50 g of Woelm neutral alumina (activity 1). Elution with 800 ml of 50:50 petroleum ether–ethyl ether and 1000 ml of ethyl ether afforded 0.8 g of **27**, mp 148–150° (total yield, 4.3 g; 75.5%). Elution of the column was continued with 500 ml of chloroform; no further materials were isolated.

6,7-Dihydro-2,4-diphenyl-1-(1-pyrrolidinyl)-3-benzothionine 3,3-dioxide (28) was afforded by direct crystallization in 65.8% yield (7.2 g), mp 218–219° dec. Analytical sample of light yellow crystals from ethanol had mp 228–229° dec; ir 1510 (en), 1270 and 1110 (both SO_2), strong bands at 747 and 690 cm^{-1}; uv max 239 (23,700) and 314 mμ (6030); nmr δ (100 MHz) 1.30–1.75 (m, 4, CH_2, pyrr), 2.00–3.00 (cp, 8, CH_2 of nine-membered ring and CH_2NCH_2), and 6.50–7.70 (cp, 15, vinyl and Ar); mass M^+ 441.

Anal. Calcd for $C_{28}H_{27}NO_2S$: C, 76.15; H, 6.16; N, 3.17. Found: C, 76.42; H, 6.33; N, 3.21.

Direct evidence for the presence of the vinyl proton in this nmr (100 MHz) was obtained using deuterated $Eu(fod)_3$. The aliphatic region was little affected; aromatic region: 6.7–7.10, 7.20–7.45, and 7.55–7.75 (three complex patterns, 6, 4, and 1, respectively, Ar), 8.05 (dd, 1, J = 11.0 and 4.0 Hz, vinyl p), and 8.30 (dd, 1, J = 2.0 Hz, Ar). Irradiation at 2.33 ppm causes collapse of the 8.05-ppm signal to a singlet with residual long-range coupling.

7,8-Dihydro-2,4-diphenyl-1-(1-pyrrolidinyl)-6*H*-3-benzothiecin 3,3-dioxide (31) was obtained in 52.5% yield (3.0 g) by direct crystallization, mp 227–229°. Analytical sample of light yellow crystals from ethanol had: mp 254–256°; ir 1518 (en), 1290 and 1121 (both SO_2), medium to strong bands at 1075, 810, 766, 758, 748, 700, 690, and 640 cm^{-1}; uv max 249 (16,500), 277 sh (7090), 287 sh (5030), 295 (5140), and 334 mμ (8290); nmr δ (100 MHz) 1.40–1.80 (m, 4, CH_2, pyrr), 2.10–2.85 (cp, 10, remaining CH_2), 6.18 [poorly resolved t (merged dd), 1, J = 8.0 Hz, vinyl p], 7.10 and 7.40 (m and s, respectively, 14, Ar). Irradiation of the sample in the nmr determination at 2.25 ppm caused collapse of the 6.18-ppm signal to a singlet; mass M^+ 455.

Anal. Calcd for $C_{29}H_{29}NO_2S$: C, 76.46; H, 6.40; N, 3.08. Found: C, 76.85; H, 6.30; N, 2.83.

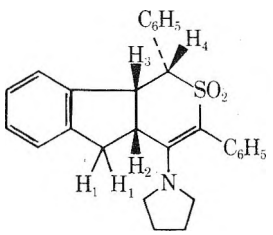
Formation of 33 and 34. Reaction of 1-Inden-3-ylpyrrolidine (32) with 5. 1-(7,7a-Dihydro-1,2-diphenylcyclobut[*a*]inden-2a-yl)pyrrolidine (33) was obtained in 55.0% yield (4.0 g), mp 168–170° dec, by triturating with ethanol (ether complexes the work-up). Analytical sample from ethanol had: mp 178–179° dec; ir 1255 (medium), 1135 (medium doublet), 760 (strong), 730 (strong), 683 cm^{-1} (strong); uv max 224 (23,000), 271 sh (10,000), 277 sh (11,600), and 294 mμ (12,700); nmr δ (60 MHz) 1.60–1.90 and 2.40–2.85 (cp, 4 each, pyrr), 2.90–3.10 (complex ABX pattern with the wings of the AB q not visible, 2, J = 4.6 and 7.0 Hz, CH_2CH), 3.94 (dd, 1, J = 4.5 and 7.0 Hz, CH_2CH), and 7.00–7.80 (cp, 14, Ar); mass M^+ 363.

Anal. Calcd for $C_{27}H_{25}N$: C, 89.31; H, 6.93; N, 3.85. Found: C, 89.38; H, 6.78; N, 3.95.

Combined filtrates on concentration and trituration with ethanol gave **1,3-diphenyl-8*H*-indeno[1,2-*c*]thiophene 2,2-dioxide (34)**: 0.7 g, (9.5% yield), mp 189–191° dec. Analytical sample from ethanol had mp 243–244° dec; ir 1275 and 1130 (both SO_2) and medium bands at 750, 725, 695, and 680 cm^{-1}; uv max 222 (20,100), 250 (20,600), 270 (20,500), 304 (8450), and 394 mμ (8290); nmr δ (60 MHz) 4.20 (s, 2, benzyl p) and 7.25–7.90 (cp, 14, Ar); mass M^+ 356.

Anal. Calcd for $C_{23}H_{16}O_2S$: C, 77.51; H, 4.53; S, 8.98. Found: C, 77.15; H, 4.49; S, 9.04.

Formation of 36 and 37. Reaction of 1-(3,4-Dihydro-2-naphthyl)pyrrolidine (35) with 5. 1,4a,5,9b-Tetrahydro-1,3-diphenyl-4-(1-pyrrolidinyl)indene[1,2-*c*]thiapyran 2,2-dioxide (37) was obtained by trituration with ether in 6.9% yield (0.5 g), mp 204–205° dec. Analytical sample by washing with acetone (or from tetrahydrofuran) had: mp 228–229° dec; ir 1548 (en), 1282 and 1118 (both SO_2), medium to strong bands at 770, 748, 722, 718, 703, and 660 cm^{-1}; uv max 266 (14,000), 273 (13,300), and 295 mμ (10,200); nmr δ (100 MHz) 1.60–1.90 (m, 4, CH_2, pyrr), 2.90–3.20 (m, 4, CH_2NCH_2), 3.29 (d, 2, $J_{1,2}$ = 10.0 Hz, 2 H_1), 3.80 (q, 1, $J_{1,2}$ = 10.0, $J_{2,3}$ = 8.0 Hz, H_2), 4.42 (t, 1, $J_{2,3} = J_{3,4}$ = 8.0 Hz, H_3), 4.65 (d, 1, $J_{3,4}$ = 8.0 Hz, H_4), 6.57 (d, 1, J = 7.0 Hz, Ar), and 6.80–7.50 (cp, 13, Ar). Irradiation of the sample in the nmr determination at the designated position caused the following changes (position of irradiation [changes]): 3.25 (H_1) [H_2 becomes a d, $J_{2,3}$ = 8.0 Hz]; 3.80 (H_2) [H_1 becomes a s; H_3 and H_4 become an AB q, J = 10.0 and 13.0 Hz]; 4.40 (H_3) [H_2 becomes a t, J = 10.0 Hz, H_4 not determined]; mass M^+ 441.



Anal. Calcd for $C_{28}H_{27}NO_2S$: C, 76.15; H, 6.16; N, 3.17. Found: C, 76.46; H, 6.09; N, 3.12.

1-(5,6-Dihydro-8,9-diphenyl-7-benzocyclooctenyl)pyrrolidine (36) was afforded by the concentration of the filtrates and trituration with ethanol–ether in 25.8% yield (1.6 g), mp 118–120°. Analytical sample of golden yellow crystals from ether–hexane had: mp 127–129°; ir 1588 and 1558 (en), 756 and 690 cm^{-1} doublet (strong olefin bands); uv max 271 (41,900), 292 (19,700), 304 (18,800), 316 sh (15,400), and 340 mμ sh (7240); nmr δ (100 MHz) 1.20–1.80 (m, 4, CH_2, pyrr), remaining aliphatic p at 1.95–2.55 (nine-line cp, 2), 2.55–3.00 (cp, 4), and 3.10–3.40 (cp, 2), and 6.65–7.70 (cp, 15, vinyl and Ar); mass M^+ 377.

Anal. Calcd for $C_{28}H_{27}N$: C, 89.08; H, 7.21; N, 3.71. Found: C, 89.40; H, 7.30; N, 3.87.

***cis-exo*-3a,4,5,6,7,7a-Hexahydro-2,3-diphenyl-7a-(1-pyrrolidinyl)-4,7-methanobenzo[*b*]thiophene 1,1-dioxide (39)** was obtained in 58.0% yield (5.5 g), mp 129–131°. Analytical sample prepared from ethyl acetate–hexane had: mp 132–134°; ir 1635, 1600 and 1575 (double bonds), 1270 and 1120 (both SO_2), and strong bands at 800, 770, 755, 722, and 700 cm^{-1}; uv max 224 (21,600) and 256 mμ sh (10,810); nmr δ (60 MHz) 1.00–2.30 (m, 11, methylene and one bridgehead p), 2.80–3.60 (m, 6, CH_2NCH_2, bridgehead p nearest the SO_2 group, according to Dreiding models, and $CHC(C_6H_5)$=CC_6H_5), and 7.00–7.60 (merging singlets centered at 7.28, 10, Ar); mass M^+ 405.

Anal. Calcd for $C_{25}H_{27}NO_2S$: C, 74.05; H, 6.71; N, 3.45. Found: C, 74.05; H, 6.96; N, 3.59.

4,5,6,7-Tetrahydro-5-methyl-2,9-diphenyl-8-(1-pyrrolidinyl)-1,5-thiazonine 1,1-dioxide (41) was obtained by direct crystallization in 37.2% yield (3.8 g), mp 142–144°. Analytical sample by washing with cold ether (0°) and ethanol (material decomposed on attempted recrystallization from benzene, methylene chloride, ethanol, and ethyl acetate) had: mp 146–148°; ir 1512 (en), 1270 (doublet) and 1113 (both SO_2), and strong band at 700 cm^{-1}; uv max 232 (14,600), 260 (10,700), and 332 mμ (6280); nmr δ 60 MHz) 1.7 (m, 4, CH_2, pyrr), 2.25–3.90 (cp with superimposed s t 2.5, 13, CH_2NCH_2 and remaining CH_2 and CH_3), and 7.00–7.80 p with two s at 7.18 and 7.46, 11, vinyl and Ar); mass M^+ 408.

Anal. Calcd for $C_{24}H_{28}N_2O_2S$: C, 70.55; H, 6.91; N, 6.86. Found: 70.86; H, 6.76; N, 6.71.

Methiodide from methanol had mp 201–203°.

Anal. Calcd for $C_{25}H_{31}INO_2S$: C, 54.50; H, 5.68; N, 4.97. Found: C, 54.45; H, 5.68; N, 5.10.

1-[2-[(1-(4-Chlorophenyl)-2-methyl-1-propenyl)sulfonyl]-2-(4-chlorophenyl)ethenyl]pyrrolidine (43b) was isolated in 63.6% yield (2.8 g), mp 144–146° [bis(4-chlorophenyl)acetylene is the major impurity, −10%]. Analytical sample obtained by chromatography on Woelm neutral alumina (eluting with ether) and subsequent recrystallization from ethanol had mp 171–172°; ir 1615 (en), 1280, 1120, and 1090 (all SO_2), weak to medium bands at 1015, 989, 956, 920, 860, 812, 714, and 668 cm^{-1}; uv max 225 (26,500), 268 sh (16,300), and 288 mμ (16,900); nmr δ (60 MHz) 1.50–2.00 [cp with two superimposed s at 1.55 and 1.95, 10, CH_2, pyrr and $(CH_3)_2C$=], 2.80–3.20 (m, 4, CH_2NCH_2), and 6.90–7.50 [AB q (one-half at 7.00, J = 10.0 Hz) with superimposed s at 7.38 (9, vinyl and Ar, J = 12.0 and 14.0 Hz)]; mass M^+ 435.

Anal. Calcd for $C_{22}H_{23}Cl_2NO_2S$: C, 60.55; H, 5.31; N, 3.21. Found: C, 60.75; H, 5.13; N, 3.21.

Formation of 44 and 45. Reaction of 1-(1-Cyclohexenyl)pyrrolidine (8) with 42. 4,5,6,7-Tetrahydro-2,9-bis(4-chlorophenyl)-3-(1-pyrrolidenyl)thionin 1,1-dioxide (44) was obtained in 88.0% yield (19.5 g), mp 125–130°. Analytical sample afforded by washing with ether had: mp 137–139°; ir 1510 (en), 1272, 1110, 1095, and 1085 (all SO_2), and medium to weak bands at 1010, 920, 818, 735, 720, 710, and 650 cm^{-1}; uv max 236 (21,300), 264 sh (12,400), 306 (6660), and 329 mμ (8040); nmr δ (100 MHz) 1.40–2.00 (m, 12, CH_2 of nine-membered and pyrr rings), 2.80–3.20 (m, 4, CH_2NCH_2), and 6.90–7.60 (cp, 9, vinyl and Ar); mass M^+ 461.

Anal. Calcd for $C_{24}H_{25}Cl_2NO_2S$: C, 61.79; H, 5.40; N, 3.00. Found: C, 61.87; H, 5.80; N, 2.86.

1,4a,5,6,7,7a-Hexahydro-1,3-bis(4-chlorophenyl)-4-(1-pyrrolidinyl)cyclopenta[*c*]thiopyran 2,2-dioxide (45) was prepared by recrystallization of **44** (1.0 g) from ethanol in 55.0% yield (0.55 g): mp 259–260° dec; ir 1575 (en), 1275, 1120, 1102, and 1090 (all SO_2), medium to weak bands at 1012, 958, 877, 845, 748, 720, and 650 cm^{-1}; uv max 230 (32,900), 265 (11,900), and 303 mμ (7770); nmr δ (100 MHz) 1.55–1.90 (cp, 10, CH_2 of fused five-membered and pyrr rings), 2.85–3.10 (cp, 6, angular methines and CH_2NCH_2), 4.12 (d, 1, α-sulfonyl p, J = 13.0 Hz, axial–axial coupling), 7.25 and 7.38 (two s, 8, Ar); a decoupling experiment located the group coupled to the α-sulfonyl proton at 3.0 ppm; mass M^+ 461.

Anal. Calcd for $C_{24}H_{25}Cl_2NO_2S$: C, 61.79; H, 5.40; N, 3.00. Found: C, 61.93; H, 5.55; N, 2.97.

6,7-Dihydro-2,4-bis(4-chlorophenyl)-1-(1-pyrrolidinyl)-3-benzothionin 3,3-dioxide (46) was obtained by direct crystallization in 90.3% yield (7.4 g), mp 210–212° dec. Analytical sample of light yellow crystals afforded from ethanol had: mp 222–224° dec; ir 1528 (en), 1279, 1118, 1097, 1089 (all SO_2), medium bands at 1012, 860, 835, 820, 752, and 715 cm^{-1}; uv max 244 (28,700), 300–312 plateau (6120), and 320 sh mμ (5900); nmr δ DMSO-d_6 (100 MHz) 1.25–1.70 (m, 4, CH_2, pyrr), 1.80–2.90 (m, 8, CH_2 of nine-membered ring and CH_2NCH_2), and 6.20–7.50 [cp with a superimposed AB q (6.34 and 6.87, J = 10.0 Hz), 13, vinyl and Ar]; mass M^+ 509.

Anal. Calcd for $C_{28}H_{25}Cl_2NO_2S$: C, 65.88; H, 4.94; N, 2.74. Found: C, 65.94; H, 4.94; N, 2.48.

1-[5,6-Dihydro-8,9-bis(4-chlorophenyl)benzocycloocten-7-yl]pyrrolidine (47) was obtained by direct crystallization and through trituration of the filtrate residue with ethanol–ether in 56.2 yield (2.0 and 3.0 g, respectively), mp 208–210° dec and 201–203° dec, respectively. Analytical sample of brilliant orange crystals from ether had mp 209–210° dec; ir 1580 and 1545 (dienamine), medium bands at 1080, 1008, and 757 cm^{-1}; uv max 213 (44,700), 274 (63,500), 308 sh (12,800), and 320 mμ sh (7160); nmr δ (100 MHz) 1.20–1.80 (m, 4, CH_2, pyrr), remaining aliphatic p at 1.95–2.60 (nine-line cp, 2), 2.60–3.00 (cp, 4), and 3.10–3.40 (cp, 2), and 6.70–7.70 (cp, 13, vinyl and Ar); mass M^+ 445.

Anal. Calcd for $C_{28}H_{25}Cl_2N$: C, 75.35; H, 5.65; N, 3.14. Found: C, 75.72; H, 5.88; N, 3.18.

Formation of 48 and 49. Reaction of 1-(1-Propenyl)pyrrolidine (6a) with 2,3-Bis(4-chlorophenyl)thiirene 1,1-Dioxide (42). 1,2-Bis(4-chlorophenyl)-1-(1-pyrrolidinyl)ethylene (49) was afforded in 25.0% yield (0.8 g), mp 118–119°. Recrystallization from ethanol gave an analytical sample: mp 122–123°; ir 1600 and 1580 (en), 1550 (aromatic double bond), and strong bands at 1395, 1345, 1085, 830, and 820 cm^{-1}; uv max 224 sh (16,100), 272 sh (10,900), 287 (16,900), 295 (16,600), 305 (18,900), and 324 mμ sh (12,900); nmr δ (60 MHz) 1.70–2.05 and 2.83–3.25 (two m, 4 and 4, $(CH_2)_2$ and CH_2NCH_2, respectively, of the pyrrolidino group),

5.25 (s, 1, vinyl p), 6.52 and 6.90 (AB q, 4, J = 10.0 Hz, Ar), and 7.25 (cp, 4, Ar); mass M^+ 317.

Anal. Calcd for $C_{18}H_{17}Cl_2N$: C, 67.93; H, 5.39; N, 4.40. Found: C, 68.26; H, 5.25; N, 4.15.

Column chromatography of the combined residues on Woelm neutral alumina (100 g), elution with 750 ml of hexane, and usual work-up with one recrystallization from ethanol gave analytically pure a 25.0% yield (1.0 g) of **1-[2,3-bis(4-chlorophenyl)-4,6-dimethylcyclohexa-2,4-dienyl]pyrrolidine (48):** mp 87–89°; ir 1580 (stilbene double bond, weak) and strong bands at 1082, 1007, and 812 cm^{-1};[28] uv max 221 mμ sh (19,800);[32] nmr δ (60 MHz) 0.98 (d, 3, CH_3CH, J = 7.5 Hz), 1.65–1.90 (cp, 7, HC=C-CH_3 and $(CH_2)_2$, pyrr), 2.5–3.1 (m, 5, CH_2NCH_2 and CH_3CH), 3.98 (d, 1, CHN<, J = 6.0 Hz), 5.78 (d further split in each portion into a t, 1, CH=CCH_3, J = 5.0 and 1.0 Hz), 6.70–7.35 (cp with superimposed s at 7.10, 8, Ar); a decoupling experiment showed that the proton at 3.98 and 5.78 were not coupled to each other; mass M^+ 3.97.

Anal. Calcd for $C_{24}H_{25}Cl_2N$: C, 72.36; H, 6.33; N, 3.52. Found: C, 72.11; H, 6.31; N, 3.56.

4,4″-Dichloro-3′,5′-dimethyl-1,1′:2′,1″-terphenyl (50). A stirred solution of 0.5 g (0.001 mol) of **48**, 0.5 g (0.003 mol) of methyl iodide, and 10 ml of methanol was heated at reflux for 3.0 hr and remained at ambient temperature overnight. Concentration *in vacuo* gave a slightly yellow solid which on washing with ethanol and filtering gave **50** in 77.0% yield (0.30 g), mp 109–110°. Analytical sample from ethanol had: mp 109–110°; ir 1600 and 1590 (both weak), 1081 (strong), 1010 (medium), 1000 (medium), and 823 cm^{-1} (strong); uv max 224 sh (26,400) and 236 mμ sh (25,200); nmr δ (60 MHz) 2.10 and 2.38 (two s, 6, CH_3) and 6.80–7.35 (cp, 10 Ar); mass M^+ 326.

Anal. Calcd for $C_{20}H_{16}Cl_2$: C, 73.40; H, 4.93. Found: C, 73.26; H, 4.86.

1,2-Bis(4-chlorophenyl)-1-(1-pyrrolidinyl)ethylene (49) was obtained in 85.0% yield (0.85 g) by treating a stirred mixture of **42** (1.0 g, 0.003 mol) and 10 ml of benzene with a solution of 0.5 g (0.007 mol) of pyrrolidine and 5 ml of benzene in one portion at 25° (reaction was evidenced by a rise in temperature to 35° and the formation of a yellow solution); solution heated at 65° for 2 hr, concentrated *in vacuo*, and triturated with cold absolute ethanol (0°) to afford a material (mp 119–120°) identical in all respects with the one isolated above.

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Registry No.—5, 5162-99-2; **6a,** 13937-88-7; **6b,** 2403-57-8; **6c,** 6908-73-2; **7a,** 52919-52-5; **7b,** 52919-53-6; **7c,** 52919-54-7; **8,** 1125-99-1; **9,** 52919-55-8; **10,** 52919-56-9; **11,** 52919-57-0; **12,** 52919-58-1; **13,** 14092-11-6; **14,** 942-81-4; **15,** 52919-59-2; **16,** 52919-60-5; **17,** 52919-61-6; **18,** 52964-36-0; **19,** 52919-62-7; **20,** 52919-63-8; **21,** 52919-64-9; **22,** 52919-65-0; **23,** 52919-66-1; **24,** 52919-67-2; **25,** 25769-05-5; **26,** 52919-68-3; **27,** 52919-69-4; **28,** 52919-70-7; **29,** 7007-34-3; **30,** 25579-44-6; **31,** 52919-71-8; **32,** 31554-37-7; **33,** 52919-72-9; **34,** 52919-73-0; **35,** 21403-95-2; **36,** 52919-74-1; **37,** 52919-75-2; **38,** 20238-06-6; **39,** 52949-88-9; **40,** 16675-55-1; **41,** 52919-76-3; **41** methiodide, 52919-77-4; **42,** 30739-21-0; **43b,** 52919-78-5; **44,** 52919-79-6; **45,** 52919-80-9; **46,** 52919-81-0; **47,** 52919-82-1; **48,** 52929-83-2; **49,** 52919-84-3; **50,** 52919-85-4; cyclodecanone, 1502-06-3; pyrrolidine, 123-75-1; cycloundecanone, 878-13-7; α,α'-sulfonylbis(α-bromo-4-chloro)toluene, 52964-37-1; bis(4-chlorophenyl)acetylene, 1820-42-4.

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(29) This process is analogous to an enamine dimerization which is well documented in the literature: G. Domschke, *Chem. Ber.*, **99**, 934 (1966).
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(32) The ultraviolet spectrum is abnormal due to the lack of coplanarity which is evident on inspection of a Dreiding model.

Dimethylsulfonium 3-Carbomethoxyallylide. Preparation and Reaction with Electrophilic Olefins to Form Substituted Vinylcyclopropanes

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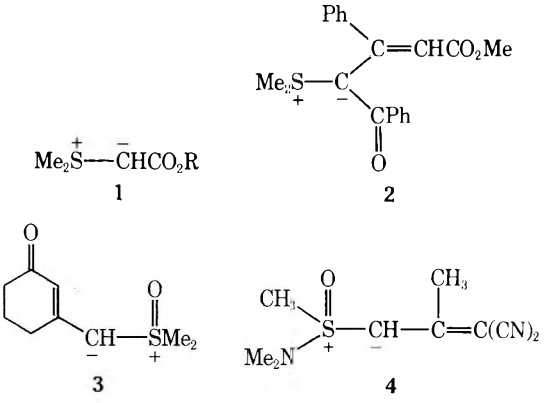
The title compound, **7**, from treatment of the corresponding sulfonium bromide, **6**, with sodium hydride and catalytic *tert*-butyl alcohol in tetrahydrofuran at 20°, has limited stability but has been treated with several Michael acceptors to produce novel vinylcyclopropanes in fair yields. One such product, **8**, has been thermally converted to a new disubstituted cyclopentene, **18**.

In recent years sulfur ylides have found a wide variety of applications in organic synthesis.[1,2] We wish to report the preparation of a new reagent in this category, dimethylsulfonium 3-carbomethoxyallylide[3a] (**7**), its reactions with electrophilic olefins to produce novel di- and trisubstituted vinylcyclopropanes, and the thermal rearrangement of one of these products to a representative new difunctional cyclopentene. Ylide **7** is a vinylog of the dimethylsulfonium carboalkoxymethylides (**1**).[4] Unsubstituted and alkyl- and aryl-substituted sulfonium allylides have also been previously investigated.[5] In addition, more highly stabilized derivatives of **7** have been reported, *e.g.*, **2**,[6] as well as oxosulfonium and aminooxosulfonium analogs, *e.g.*, **3**[2c,7] and **4**.[8]



Results

3-Carbomethoxyallyldimethylsulfonium bromide (**6**) was prepared in 95% yield by treatment of methyl 4-bromocrotonate[9] (**5**) with excess dimethyl sulfide in acetone at room temperature. The nmr spectrum of **6** showed its configuration to be >95% trans. Conversion of the sulfonium salt to ylide **7** was achieved by reaction with sodium hydride in tetrahydrofuran (THF) in the presence of 0.05 equiv of *tert*-butyl alcohol under high-turbulence stirring at 20–22°. The ylide **7** has limited stability, decomposing to an intractable brown residue if allowed to stand at room temperature for 1 hr. It may be effectively utilized, however, by adding substrate immediately after generation of the ylide solution (cessation of hydrogen evolution).

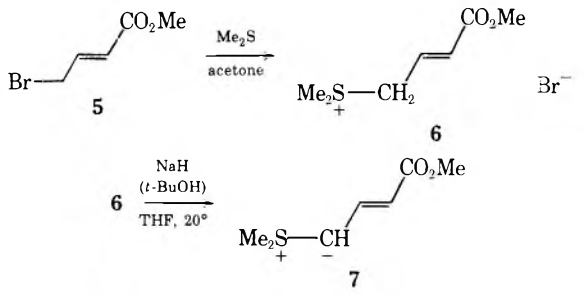
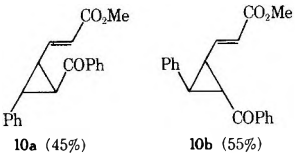
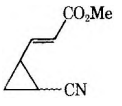
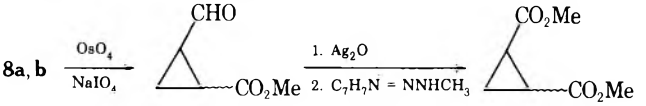


Table I
Vinylcyclopropanes from Ylide 7

Substrate	Products	Yield, %
Methyl acrylate	**8a** (3%), **8b** (97%)	50
Dimethyl fumarate	**9**	57
Dimethyl maleate	**9**	60
Benzalacetophenone	 **10a** (45%) **10b** (55%)	50
Acrylonitrile	 **11**	20

Reaction of **7** with 1.0 equiv of several Michael acceptors produced the cyclopropane products presented in Table I. All are previously unreported compounds. The reactions were conducted at room temperature overnight, followed by conventional work-up.

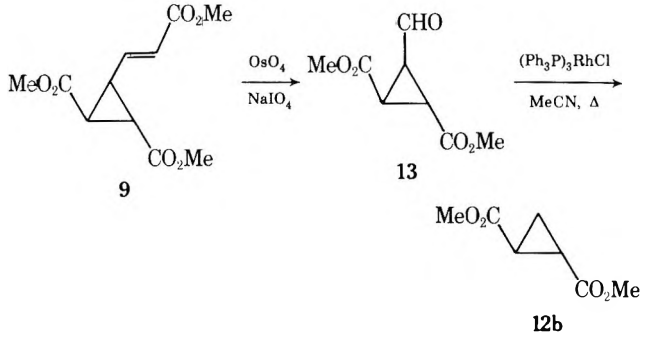
In this manner, methyl acrylate gave in 50% distilled yield a liquid product, bp 91–94° (2 mm), identified as 3% *cis*- and 97% *trans*-1-(*trans*-2-carbomethoxy)vinyl-2-carbomethoxycyclopropane, **8a** and **8b**, respectively. The constitution and double-bond configuration of **8** were determined by ir, nmr, and mass spectra and elemental analysis. Gas chromatography (gc) of the known degradation products dimethyl *cis*- and *trans*-1,2-cyclopropanedicarboxylate,[10] **12a** and **12b**, respectively, obtained by double-bond cleavage, oxidation, and esterification, established the ring-configurational composition.



12a, cis, 3%
12b, trans, 97%

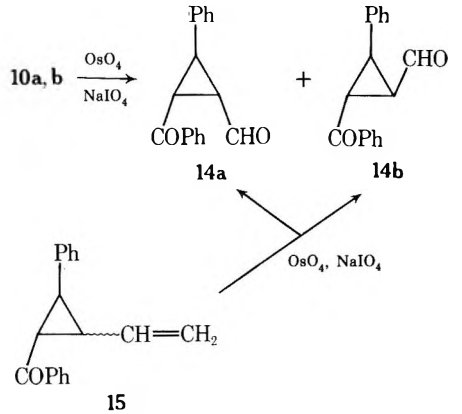
Reaction of **7** likewise with dimethyl fumarate generated a liquid product, bp 127–129° (0.12 mm), shown to be 1-(*trans*-2-carbomethoxy)vinyl-*trans*-2,3-dicarbomethoxycyclopropane (**9**). The assigned structure was supported by spectral data and elemental analysis, the nmr spectrum indicating only trans vicinal proton coupling across the double bond. The ring configuration in **9** was established by side-chain cleavage to produce a single aldehyde, **13**, whose nmr spectrum exhibited two methyl ester signals and which was decarbonylated[11] with tris(triphenylphosphine)chlororhodium to give only *trans*-1,2-dicarbomethoxycyclopropane, **12b**.

Similar reaction of ylide **7** with dimethyl maleate afforded in 60% yield after distillation the same product, **9**, as that from dimethyl fumarate, on the basis of ir and nmr spectra. Degradation of the product from maleic ester in the same fashion as that from fumarate, above, again yielded only *trans*-cyclopropane diester **12b**.



9 **13** **12b**

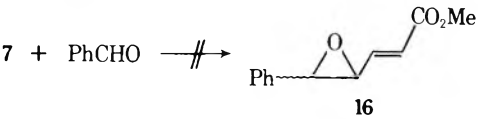
Reaction between **7** and benzalacetophenone gave rise to a crude yellow oil which partially solidified on standing. Its monomeric content was indicated by degradation to be 45% methyl *trans*-3-(*cis*-2-benzoyl-*trans*-3-phenylcyclopropyl)-acrylate (**10a**) and 55% of the trans,trans,cis isomer, **10b**. Treatment of the crude product with osmium tetroxide–sodium metaperiodate produced a mixture of two aldehydes whose combined nmr spectrum was in accord with those of the separate isomeric aldehydes **14a** and **14b** obtained by Trost and coworkers[5e] from a similar degradation of isomeric 1-benzoyl-2-phenyl-3-vinylcyclopropanes (**15**). The **10a/10b** product ratio was taken to be that of the integrated aldehydic proton absorptions. A small amount (10% yield) of the major product, **10b**, was isolated as colorless needles, mp 109.0–110.0°, which had spectral properties and elemental analysis in agreement with the assigned structure. The yield of **10a,b** is estimated to be *ca.* 50%.



14a **14b** **15**

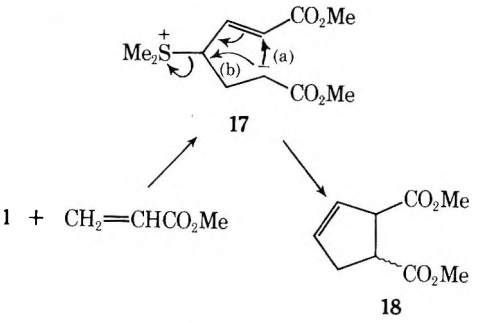
Less definitive results were obtained for reaction between **7** and acrylonitrile. Distillation of the product gave material of bp 109–116° (1.5 mm), in 32% yield for the anticipated vinylcyclopropanes. Isolation of the major gas-chromatographic fraction from a nonpolar column led to nmr evidence for 1-cyano-2-(*trans*-2-carbomethoxyvinyl)cyclopropane (**11**) (probably both isomers), as the principal product structure (*ca.* 20% yield). Addition of chemical shift reagent $Eu(fod)_3$[12] to the product mixture, however, allowed the resolution of six carbomethoxy proton signals. The minor products were not identified. It may be noted that anomalous results have been obtained in reactions of other sulfur ylides with α,β-unsaturated nitriles.[4d,13]

In view of the reactions of other sulfur ylides with carbonyl compounds to form epoxides,[1,2] reaction of **7** with benzaldehyde was undertaken. Nmr examination of the crude product, however, showed the presence of unreacted benzaldehyde and ylide decomposition products only; no evidence for the oxirane, **16**[2i], was found.

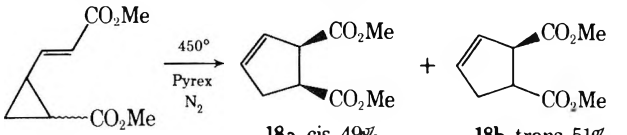


16

Our interest in ylide **7** was based on its potential for five-membered as well as three-membered carbocyclic ring synthesis with electrophilic olefins. Cyclopentene derivatives could be envisioned either from SN2′ ring closure subsequent to Michael addition, *e.g.*, **7** → **17** (path a) → **18**, or by the thermal rearrangement[14] of vinylcyclopropane products, *e.g.*, **8** → **18**.



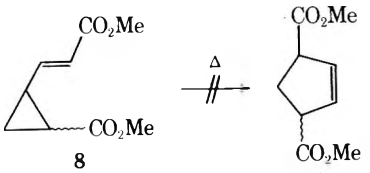
In fact, no cyclopentenoid products were detected from any of the reactions listed in Table I. Flow pyrolysis of product **8** over Pyrex beads at 450°, however, did provide a useful route to the cyclopentene system **18**. Distillation of



8a, cis, 3%
8b, trans, 97%

18a, cis, 49% **18b**, trans, 51%

the pyrolysate provided material of bp 101–105° (2 mm) shown to contain *cis*- and *trans*-3,4-dicarbomethoxycyclopentene, **18a** and **18b**, respectively, in a 49:51 ratio and 64% yield, plus 16% of unconverted **8**. Nmr integration showed the rearrangement product to possess two vinylic protons, ruling out double-bond position isomers of **18**. The constitution and configurational composition of **18** were established by hydrogenation to the corresponding *cis*- and *trans*-cyclopentane-1,2-dicarboxylic esters, whose gc retention times and spectra matched those of authentic samples. Alternative rearrangement **8** → **19** by cleavage of the bond between the side chain and methylene carbons was shown not to have occurred; *cis*- and *trans*-3,5-dicarbomethoxycyclopentenes **19** were prepared independently and shown by gc to be absent from the distilled pyrolysis product.

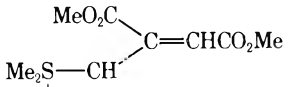


8 **19a**, cis **b**, trans

Discussion

Carbomethoxyallylide **7** exhibits reactivity similar to that of the parent ester- and ketone-stabilized sulfonium ylides, $Me_2S^+C^-HCO_2R$, **1**, and $Me_2S^+C^-HCOPh$. Characteristically, these ylides add to electrophilic olefins to produce cyclopropanes[4c,d,h,6,15] but fail to generate oxiranes

from simple aldehydes and ketones.[4b,m,6,15-18] Oxosulfonium analog **3**, for comparison, is likewise useful for the formation of cyclopropanes from Michael acceptors,[2c] while the highly delocalized sulfonium ylide **2** is without apparent reagent properties.[6] An additional structural relative of **7**, dimethylsulfonium 2,3,-dicarbomethoxyallylide (**20**), is a



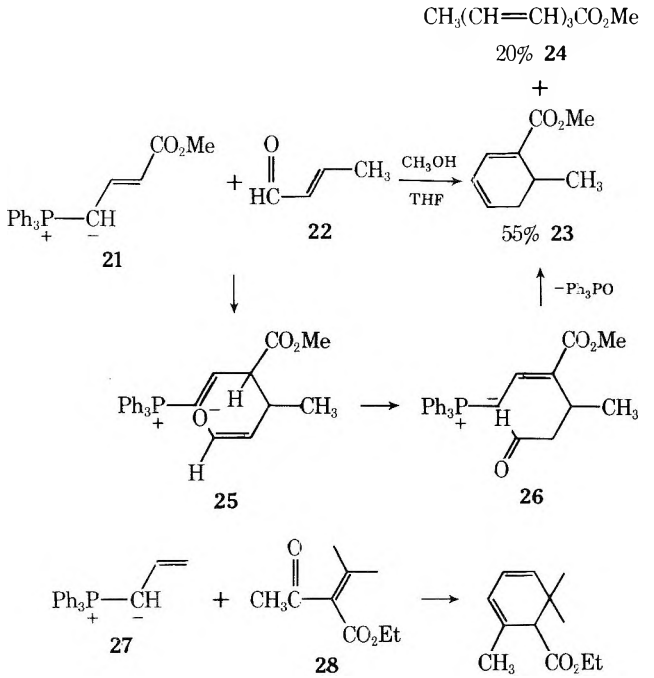
20

hypothetical intermediate in base-induced coupling of the corresponding sulfonium ion but has not been generated as an independent reagent.[3]

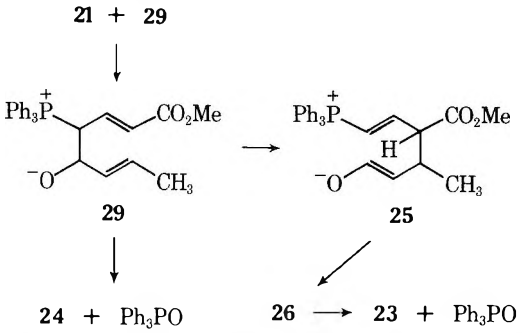
The reactions of **7** reported here are somewhat compromised by concurrent decomposition of the ylide. They are nevertheless of preparative importance, as the products are otherwise unknown polyfunctional compounds capable of diverse further transformations. It is likely that alternative base–solvent conditions can be found[1f,g,2a] to effect improved yields in reactions of **7**.

Betaines have been strongly implicated as intermediates in sulfur ylide reactions with electrophilic double bonds,[1,2f,4l,13] *e.g.*, **17** (path b) in the present instance. That both maleic and fumaric ester lead from ylide **7** to the same product, **9**, indicates that conformational equilibration in the corresponding intermediates is faster than ring closure, a situation reported for other reactions of stabilized ylides.[2g,4c,19,20] The system was not tested for maleate → fumarate conversion by reversible Michael addition.[2f,19]

A noteworthy contrast exists between the present reactions of sulfonium ylide **7** and those reported recently by Bohlmann and Zdero[21] for the triphenylphosphonium analog, **21**. With α,β-olefinic carbonyl compounds ylide **21** produces 1-carbomethoxy-1,3-cyclohexadienes as principal products, *e.g.*, **23**, along with minor amounts of normal Wittig products, *e.g.*, **24**. Büchi and Wüest[22] had earlier observed the abnormal reaction for the parent triphenylphosphonium allylide, **27**, and α-carbethoxyenone **28**. Both groups postulated the cyclization pathway to proceed by Michael addition on the part of the carbon γ to phosphorus, followed by activated hydrogen transfer to enolate oxygen and intramolecular Wittig reaction of the resultant aldehyde or ketone, as illustrated for **21**.



We would suggest an alternative mechanism, whereby both products emanate from initial carbonyl addition by the allylide α carbon. The first intermediate in this case, **29**, could partition itself between normal elimination of triphenylphosphine oxide, to produce **24**, and [3,3] sigmatropic rearrangement to **25**, which would lead to cyclized product **23** as previously proposed. This mechanism accords



with the characteristic 1,2 addition of representative Wittig reagents with conjugated enones and enals;[23] only in cases of pronounced steric hindrance around carbonyl is 1,4 addition observed.[23] Initial formation of **29**, moreover, would represent greater nucleophilicity of the phosphonium allylide at its α rather than γ carbon, a property established for sulfonium allylides here by product structures.[24] For rearrangement **29** → **25**, in competition with normal Wittig elimination, driving force would be provided by stabilization through conjugation of both the anionic and cationic[22,25] centers.[26-28]

The thermal rearrangement of vinylcyclopropane **8** to cyclopentene **18** proceeds, as generally observed, with cleavage of only the more substituted eligible ring bond[14,g,l,n] and without the stereospecificity associated by orbital symmetry conservation[29] with a concerted sigmatropic reaction.[14d-f,i,j,n] For the symmetry-allowed pathway suprafacial with respect to the allyl moiety and with inversion of configuration at the migrating carbon, **8b** should produce wholly **18b**.[29] Doering and Sachdev have recently interpreted detailed related results in terms of a continuous diradical transition state.[14n]

Cyclopentene diester **18**, although produced nonstereospecifically, has a constitution suggestive of useful applications to prostaglandin synthesis.[30,31]

Experimental Section

General. Melting points (uncorrected) were obtained in capillary tubes with a Thomas-Hoover apparatus. Nuclear magnetic resonance (nmr) spectra were recorded on either a Varian A-60A or HA-100 spectrometer, using solutions in $CDCl_3$ or CCl_4 with internal tetramethylsilane. Infrared (ir) spectra were recorded on a Beckman IR-8 instrument either as thin films or as *ca.* 2% solutions in CCl_4. Mass spectra were obtained using a Varian M-66 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Analytical gas chromatography was performed with a Wilkens Aerograph Hy-Fi Model 600-C instrument with flame-ionization detector. The following columns were employed throughout most of this work, using nitrogen as the carrier gas at 20 psi: (A) 5-ft × ⅛-in. 10% butanediol adipate on 70–80 mesh Anakrom ABS (Analabs, Inc.); (B) 10-ft × ⅛-in. 10% butanediol adipate on 70–80 mesh Anakrom ABS; (C) 5-ft × ⅛-in. 2% SE-30 on 60–80 mesh Chromosorb G (acid washed, DMCS treated).

Methyl 4-bromocrotonate was prepared as described by Vogel[9] from methyl crotonate and *N*-bromosuccinimide.

3-Carbomethoxyallydimethylsulfonium Bromide (6). In a 250-ml round-bottomed flask was placed a mixture of 20.0 g (0.112 mol) of methyl 4-bromocrotonate, 14.0 g (0.224 mol) of dimethyl sulfide, and 50 ml of dry acetone. The flask was stoppered and magnetically stirred at room temperature for 48 hr. A quantitative yield of the white hygroscopic crystalline product was collected by vacuum filtration under nitrogen in a glove bag, mp 94.5–95.5°: ir

($CHCl_3$) 1741, 1661, 1251, 1041 cm^{-1}; nmr (60 MHz, $CDCl_3$) δ 6.68 (m, HC=CH), 5.01 (d, CH_2), 3.82 (s, CO_2CH_3), 3.40 (s, $S^+(CH_3)_2$). In $CDCl_3$ solution, the salt was observed by nmr to revert predominantly over several hours to methyl *trans*-4-bromocrotonate and dimethyl sulfide. Crystalline **6** was further found to decompose over several days under dry nitrogen to a white solid, not identified, insoluble in chloroform.

Dimethylsulfonium 3-Carbomethoxyallylide (7). A 1000-ml three-necked creased (Morton) flask was equipped with a thermometer, a high-speed mechanical stirrer (G. K. Heller Co., Las Vegas, Nev., Model GT 21), and a gas-outlet tube leading to a tetrahydrofuran (THF) bubbler. In the flask was placed 350 ml of dry (4A molecular sieves) THF, 0.33 g (4.5 mmol) of *tert*-butyl alcohol, and 2.17 g (0.091 mol) of sodium hydride (3.56 g of a 61% mineral oil dispersion, washed twice with either anhydrous ether or hexane). 3-Carbomethoxyallyldimethylsulfonium bromide, **6**, (21.0 g, 0.087 mol), was weighed under nitrogen and transferred in one step to the stirred reaction mixture. The reaction temperature was maintained at 20–22° by means of a water bath, and the reaction mixture was stirred rapidly until hydrogen evolution had virtually ceased (*ca.* 2 hr). At this point the ylide solution was amber-yellow, but it turned brown if allowed to stand for 1 hr. Attempts to isolate the ylide by filtration of the solid and rotary evaporation of the solvents afforded only an undefinable brown residue.

Dimethyl *cis*- and *trans*-1,2-Cyclopropanedicarboxylate. The diesters were prepared by the method of McCoy.[10] They were readily separated as the corresponding diacids, the cis isomer being purified *via* the internal anhydride.

Dimethyl *cis*- and *trans*-1,2-Cyclopentanedicarboxylate. These diesters were prepared by the method of Latont and Bonnet[32] and separated in the same manner as the cyclopropane diesters.

Dimethyl *cis*- and *trans*-Δ^4-1,3-Cyclopentenedicarboxylate. The cis diester was obtained from the ozonolysis at −78° of norbornadiene followed by silver oxide oxidation and esterification, following the procedure of Grob and Pfaendler.[33] The trans diester was obtained in an equilibrium mixture with the cis by treatment of the latter with boiling methanolic sodium methoxide.

Reaction of Ylide 7 with Methyl Acrylate. Immediately after generation of the ylide solution (from 0.087 mol of sulfonium salt) using the technique described above, 7.49 g (0.087 mol) of methyl acrylate in 25 ml of THF was added in one portion. Moderate stirring was continued at room temperature for 16 hr. The reaction mixture was then poured into 1000 ml of water and transferred to a 3-l. separatory funnel. The aqueous layer was extracted with two 200-ml portions of ether, and the combined ether extract was washed once with 100 ml of water and then dried over anhydrous magnesium sulfate. Removal of the solvents on the rotary evaporator gave an amber liquid which after distillation through a heated 60-cm single-tantalum-helix column afforded 8.0 g (50%) of a clear colorless liquid, bp 91–94° (2 mm): ir (thin film) 3025, 2965, 1715, 1650, 1445, 1265, 1205, 1180, 1155 cm^{-1}; nmr (60 MHz, CCl_4) δ 6.42 (m, HC=CH), 5.85 (d, HC=CH, J = 15 Hz), 3.63 (s, CO_2CH_3), 2.47–0.93 (m, ring H); mass spectrum *m/e* 184 (molecular ion). *Anal.* Calcd for $C_9H_{12}O_4$: C, 58.70; H, 6.58. Found: C, 58.82; H, 6.64.

In a 100-ml round-bottomed flask was placed 1.0 g (5.44 mmol) of the product, **8**, and 24 ml of 3:1 dioxane–water. Approximately 20 mg of crystalline osmium tetroxide was added to this magnetically stirred solution,[34] and after several minutes the reaction mixture turned black. At this time 2.56 g (11.95 mmol) of sodium metaperiodate was added to the reaction mixture in small portions over 0.5 hr. After the addition the reaction was stirred at 25° for 3.5 hr and then suction filtered, and the salts were washed well with ether. The combined filtrate and washings were concentrated by rotary evaporation, and the residue was taken up in ether–water and transferred to a separatory funnel. The layers were separated and the aqueous phase was extracted with two additional 50-ml portions of ether. The combined ether extract was washed with 50 ml of brine, filtered through neutral alumina, and dried over anhydrous magnesium sulfate. Rotary evaporation of the solvent afforded 0.56 g of a residual crude yellow-brown oil, which had nmr properties (60 MHz, CCl_4) consistent with the expected aldehyde: δ 9.25 (d, J = 4 Hz, CHO), 3.65 (s, CO_2CH_3), 2.13 (m, ring H), 1.33 (m, ring H).

To a cold, magnetically stirred suspension of silver oxide (prepared by adding 1.06 g (6.26 mequiv) of silver nitrate to 0.25 g (6.26 mequiv) of sodium hydroxide in 20 ml of water) was added over a 5-min period the crude aldehyde (3.13 mmol, based on the assumption of 0.40 g of aldehyde). After stirring at 0° for 10 min, 0.63 *M* sodium hydroxide was slowly added until the solution was slightly alkaline (5.2 ml, 3.27 mequiv). The black silver metal was filtered (room pressure) and washed well with water. The resulting clear solution was then cooled and acidified to *ca.* pH 3 with 10% hydrochloric acid. The cloudy acidic layer was extracted with four 50-ml portions of ether, and the combined ether extract was washed once with water and dried over magnesium sulfate. Rotary evaporation of the ether gave 0.45 g of a yellow oil, which had nmr properties in accord with the expected acid (60 MHz, CCl_4): δ 9.01 (s, CO_2H), 6.36 (s, CO_2CH_3), 2.12 (m, ring H), 1.32 (m, ring H).

In a 100-ml three-necked round-bottomed flask fitted with condenser, magnetic stirrer, and addition funnel was placed 0.45 g (3.12 mmol) of crude acid in 10 ml of anhydrous ether. To this stirred solution was added *via* the addition funnel 0.51 g (3.43 mmol) of 1-methyl-3-*p*-tolyltriazene (Willow Brook Laboratories, Inc., with accompanying data sheet) in 10 ml of ether. The reaction mixture was stirred at room temperature for 15 min and then boiled at reflux for 4 hr. After cooling to room temperature, the reaction mixture was transferred to a separatory funnel with the aid of additional ether and washed successively with two 25-ml portions of 10% hydrochloric acid, two 25-ml portions of 10% aqueous sodium bicarbonate, and once with 25 ml of water. After drying (magnesium sulfate), rotary evaporation gave 0.3 g of a slightly yellow liquid. Gas chromatography using column A at 150° revealed the presence of two components, identified as 97% *trans*- and 3% *cis*-dimethyl 1,2-cyclopropanedicarboxylate by comparison of retention times with those of the independently synthesized compounds (above). The nmr spectrum essentially matched that of the authentic trans diester (60 MHz, CCl_4): δ 3.65 (s, CO_2CH_3), 2.07 (m, ring H), 1.25 (m, ring H).

Reaction of Ylide 7 with Dimethyl Fumarate. To a freshly prepared ylide solution (from 0.087 mol of sulfonium salt, **6**) was added 12.6 g (0.087 mol) of dimethyl fumarate (Eastman) in 100 ml of THF, and the reaction was stirred at room temperature for 16 hr. After work-up (see above) there was obtained 19.2 g of brown viscous liquid. This material was distilled through a heated 60-cm single-tantalum-helix column to give 12.0 g (57%) of a very viscous, clear, colorless liquid (which turned cloudy upon standing), bp 127–129° (0.12 mm). Gas chromatography showed this material to be homogeneous: ir (thin film) 3080, 2970, 1720, 1655, 1445, 1330, 1260, 1180, 1140 cm^{-1}; nmr (60 MHz, $CDCl_3$) δ 6.92 (m, HC=CH), 6.10 (d, HC=CH, J = 16 Hz), 3.75 (s, CO_2CH_3), 2.57 (m, ring H); mass spectrum *m/e* 242 (molecular ion). *Anal.* Calcd for $C_{11}H_{14}O_6$: C, 54.50; H, 5.84. Found C, 54.73; H, 6.00.

Oxidation of 1.0 g (4.14 mmol) of the product (**9**) was conducted with catalytic osmium tetroxide and 1.95 g (9.1 mmol) of sodium metaperiodate, as described above, to yield after work-up 0.82 g of a yellow oil which had the nmr properties expected for aldehyde **13** (100 MHz, CCl_4): δ 9.28 (d, CHO, J = 5.5 Hz), 3.73 (s, CO_2CH_3), 3.72 (s, CO_2CH_3), 2.92 (t, ring H, J = 5.5 Hz), 2.50 (m, ring H). Only one aldehydic and two $-CO_2CH_3$ absorptions were observed in the nmr spectrum even with added $Eu(fod)_3$.[12] Gas chromatography showed only one component.

In a 25-ml round-bottomed flask with reflux condenser and magnetic stirrer was placed 50 mg (0.269 mmol) of the aldehyde, **13**, and 5 ml of acetonitrile.[11] This solution was then brought to a boil under reflux, and 0.25 g (0.269 mmol) of tris(triphenylphosphine)rhodium (I) chloride (Ventron) was added in small portions over a 1-day period. After boiling at reflux for 4 days, reaction was shown by gc to be complete. The acetonitrile was removed on the rotary evaporator and the residue taken up in EtOH and filtered. The filtrate was concentrated, taken up in ether, and filtered again. Concentration of the ethereal solution by rotary evaporation gave a yellow liquid. Gas chromatographic analysis of this liquid showed that the only product was dimethyl *trans*-1,2-cyclopropanedicarboxylate, **12b**, by comparison of retention time and nmr spectrum with those of authentic compound (see above).

Reaction of Ylide 7 with Dimethyl Maleate. This reaction was carried out as before using 10.0 g (0.0415 mol) of sulfonium salt **6** and 6.0 g (0.0415 mol) of dimethyl maleate in 30 ml of THF. After work-up 8.0 g of a yellow, viscous liquid was obtained. Short-path distillation afforded 6.0 g (60%) of a colorless, viscous liquid (which became slightly turbid upon standing), bp 140–145° (0.6 mm), homogeneous by gc. The ir and nmr spectra of this compound were identical with those of the product from the reaction with dimethyl fumarate.

Oxidative degradation and decarbonylation were carried out as with the fumarate-derived product, again producing aldehyde **13** and only the trans diester **12b**, by nmr and gc criteria.

Reaction of Ylide 7 with Benzalacetophenone (Chalcone).

To a freshly prepared ylide solution (from 0.087 mol of sulfonium salt **6**) was added 18.1 g (0.087 mol) of chalcone (Aldrich) in 25 ml of THF, and the reaction mixture was stirred for 16 hr. After work-up, 25 g of a viscous yellow oil was obtained which partially solidified upon standing. Collection and recrystallization of the solid material from ether–pentane yielded 2.5 g (8.7 mmol, 10%) of white solid, mp 109–110°: ir (CCl_4) 3090, 3060, 2970, 1730, 1680, 1655, 1260, 1150, 1035, 705 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.97 (m, aromatic H), 7.43 (m, aromatic H), 7.20 (broad s, aromatic H), 6.35 (m, HC=CH), 5.88 (d, HC=CH, J = 15 Hz), 3.57 (s, CO_2CH_3), 3.25 (m, ring H), 2.68 (m, ring H). *Anal.* Calcd for $C_{20}H_{18}O_3$: C, 78.40; H, 5.93. Found C, 78.06; H, 5.94.

Attempted refinement of the remaining oily product by crystallization and by chromatography was unsuccessful (evidently the consequence of closely similar amounts of isomers **10a** and **10b**).

Identification of the pure crystalline product as **10b** was carried out by oxidative degradation with osmium tetroxide and sodium periodate, as described above, to produce aldehyde **14b**, whose nmr spectral properties were fully in accord with those listed for this compound by Trost, *et al.*[5e]

The composition of the original oily product mixture (before separation of the crystalline component) was determined by side-chain cleavage of 1.34 g of this material in the same manner to yield after work-up 0.47 g of brown oil, whose nmr spectrum was a composite of those reported[5e] for **14a** and **14b**. The vinylcyclopropane product ratio was taken to be that of the derived aldehydes by nmr integration in the –CHO region, 45% **14a** (δ(CHO) 9.57, J = 6.0 Hz) and 55% **14b** (δ(CHO) 9.15, J = 5.0 Hz).

Reaction of Ylide 7 with Acrylonitrile. To a freshly prepared ylide solution (from 0.087 mol of sulfonium salt) was added 4.87 g (0.087 mol) of acrylonitrile in 25 ml of THF, and the reaction was stirred for 16 hr. After work-up there remained 10.3 g of a viscous amber liquid, which upon distillation through a 60-cm single-tantalum-helix column afforded 4.15 g (32%) of a clear colorless liquid, which turned cloudy upon standing, bp 109–116° (1.5 mm). The product was purified by slow filtration through coarse-grade filter paper to remove a small amount of another liquid phase. The major component of this product was obtained enriched but not pure by preparative gas chromatography (5-ft × ⅜-in. SE-30 on Chromosorb W): ir (thin film) 3043, 2975, 2873, 2253, 1717, 1658, 1445, 1272, 1214, 1159 cm^{-1}; nmr (60 MHz, $CDCl_3$) δ 6.22 (m, HC=CH), 3.70 (broad s, CO_2CH_3), 2.20 (m, ring H), 1.37 (m, ring H). The impure nature of the product precluded elemental analysis.

Reaction of Ylide 7 with Benzaldehyde. To a freshly prepared solution of ylide (from 0.087 mol of sulfonium salt) was added 9.22 g (0.087 mol) of benzaldehyde in 20 ml of THF, and the reaction mixture was stirred for 16 hr. After work-up there was obtained a yellow liquid, indicated by nmr to contain essentially only unreacted benzaldehyde and ylide decomposition products.

Pyrolysis of 1-(*trans*-2-Carbomethoxy)vinyl-2-carbomethoxycyclopropane (8a,b). Vinylcyclopropane **8** (4.0 g, 0.017 mol) was added dropwise from an addition funnel onto a 35-cm Pyrex-bead-packed column maintained at 450° and under a slow stream of nitrogen. The product was collected in a 100-ml three-necked flask fitted with a Dry Ice condenser and containing 25 ml of ether cooled to −78°. After the pyrolysis, the ether was evaporated, and the crude residue was distilled through a short-path column, yielding 3.2 g (80%) of a clear colorless liquid, bp 101–105° (2 mm). Gc of the reaction mixture using column C at 120° showed one major peak (relative area 80) and two overlapping minor peaks (combined area 20). The principal minor constituent had the same retention time as that of the starting material, **8b**. On column B at 175° the major product was resolved into two peaks, shown to be cyclopentenes **18a,b**, as follows.

The predominant signals in the integrated nmr spectrum (60 MHz, CCl_4) of the distilled product were appropriate to a dicarbomethoxycyclopentene with two vinylic protons: δ 5.65 (m, HC=CH), 3.65 (s, CO_2CH_3), 3.57 (m, ring H), 3.25 (m, ring H), 2.63 (m, ring H). Hydrogenation of 0.6 g of product, at 60 psi over 5% palladium-on-charcoal in ether, produced a liquid whose two major components had gc retention times identical with those of *cis*- and *trans*-1,2-dicarbomethoxycyclopentane (see above) in the ratio of 49:51, respectively. The assignments were reinforced by essentially matching nmr spectra of the hydrogenation product (taking account of impurities) and a 1:1 mixture of the authentic epimeric cyclopentane diesters.

The absence (<0.5%) of the constitutionally isomeric diesters **19a,b** was established cleanly by gc comparison with the authentic compounds (see above) using column B at 175°.

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Registry No.—**6**, 52919-94-5; **7**, 52919-95-6; **8a**, 52919-96-7; **8b**, 52949-89-0; **9**, 52919-97-8; **10a**, 52919-98-9; **10b**, 52949-90-3; *cis*-**11**, 52919-99-0; *trans*-**11**, 52949-91-4; **12a**, 826-34-6; **12b**, 826-35-7; **13**, 52920-00-0; **14a**, 27557-63-7; **14b**, 27557-62-6; **18a**, 52949-92-5; **18b**, 52949-93-6; methyl acrylate, 96-33-3; dimethyl fumarate, 624-49-7; dimethyl maleate, 624-48-6; chalcone, 94-41-7; acrylonitrile, 107-13-1; methyl *trans*-4-bromocrotonate, 6000-00-6; dimethyl sulfide, 75-18-3; *cis*-1-carbomethoxy-2-formylcyclopropane, 52920-01-1; *trans*-1-carbomethoxy-2-formylcyclopropane, 35501-84-9; *cis*-1,2-cyclopropanedicarboxylic acid monomethyl ester, 31420-47-0; *trans*-1,2-cyclopropanedicarboxylic acid monomethyl ester, 52920-02-2; benzaldehyde, 100-52-7.

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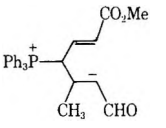

30

from **21** + **27**, because of its inferior leaving group,[1a] resulting in reversion to reactants and slower but productive formation of **25**. We would favor the alternative mechanism proposed in the text on the basis of the typical preference of Wittig reagents for 1,2 addition to enones and enals.
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Synthesis and Reactions of 5-Cyclononynone

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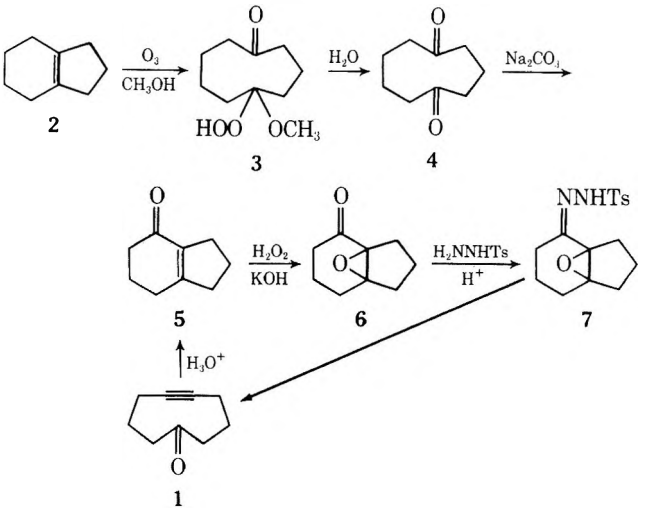
The previously unknown 5-cyclononynone (1) has been synthesized in an overall yield of 20% from 4,5,6,7-tetrahydroindan (2). As part of the synthesis, a very effective method of preparing bicyclo[4.3.0]-1(6)-nonen-2-one (5) has been developed. Fragmentation of the tosylhydrazone of the α,β-epoxy ketone **6** gave directly the strained cycloalkynone **1**. A number of reactions of **1** have been investigated, including partial hydrogenation to yield *cis*-5-cyclononenone (**10**), which in turn could be converted by photoisomerization to *trans*-5-cyclononenone (**11**). A Diels–Alder reaction of **1** with 2,5-dimethyl-3,4-diphenylcyclopentadienone (**12**) resulted in the formation of the novel adduct **13**. Acid-catalyzed transannular cyclization of **1** gave the bicyclic ketone **5** as the only product. All attempts to show that the optically active *l*-menthydrazone of **1** was a mixture of two diastereomers, because of the restricted rotation in the nine-membered ring, were unsuccessful.

A recent review[1] on the synthesis of cycloalkynes of medium sized rings indicated that no cyclononynone had yet been reported although 5-cyclodecynone had been prepared[2] and a Diels–Alder adduct of the very reactive 2-cyclooctynone had been isolated.[3] This report outlines the synthesis of the strained 5-cyclononynone (**1**) and describes a number of its reactions.

Synthesis of 5-Cyclononynone (1). The synthetic approach employed the well-known fragmentation reaction of the tosylhydrazone of an α,β-epoxy ketone.[2] The required ketone (**6**) was prepared from 4,5,6,7-tetrahydroindan (**2**) as outlined in Scheme I. Ozonolysis of **2** in methanol would be expected to yield hydroperoxide **3** which upon treatment with water would hydrolyze to **4**, analogous to the ozonolysis of 9,10-octalin in methanol as reported by Criegee.[5-7] After this ozonolysis procedure no attempt was made to purify diketone **4** as previous reports[8] indicated it very readily underwent intramolecular aldol condensation. Thus, treatment of our hydrolyzed ozonolysis product with aqueous sodium carbonate solution gave the unsaturated ketone **5** in 50% yield from **2**. This preparation of **5** is superior both in availability of starting material and overall percentage yield to those procedures previously reported.[9]

Epoxy ketone **6** was readily prepared from **5** by treatment with alkaline hydrogen peroxide.[10] Reaction of **6** with

Scheme I

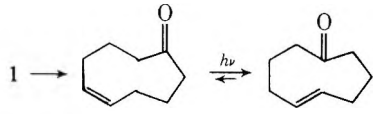


2 **3** **4** **5** **6** **7** **1**

tosylhydrazine in acetic acid–methylene chloride at −20° followed by warming to room temperature gave 5-cyclononynone (**1**) in 56% yield. All the spectral properties are consistent with this structure (see Experimental Section). In the infrared spectrum of **1** no absorption for –C≡C–

stretching is found in the 2200-cm^{-1} region because of the symmetry of the molecule[11] but the reactions to be discussed leave no doubt that a triple bond is present. The sequence described accomplishes in an overall yield of 20% from **2** the synthesis of the previously unknown 5-cyclononynone (**1**). Unlike 2-cyclooctynone,[3] this strained system is stable at room temperature. Possibly 4-cyclooctynone could be prepared using the same approach and it would be of interest to ascertain if this compound were as unstable as the 2 isomer.

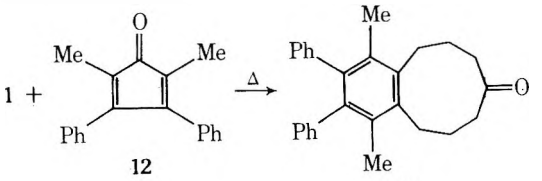
Reactions of 5-Cyclononynone (1). Hydrogenation of **1** in the presence of 5% Pd on charcoal resulted in the uptake of 2 mol of hydrogen and the formation of cyclononanone as the only product, thus confirming the carbon skeleton of **1**. When Brown's nickel boride (P2) catalyst[12] was used the rate of hydrogen uptake decreased sharply after the addition of 1 mol and *cis*-5-cyclononenone (**10**) was obtained in high yield. Uv irradiation of **10** with a 300-nm source resulted in the establishment of a photoequilibrium mixture consisting of 80% *trans*-5-cyclononenone (**11**) and 20% **10**. The ir spectra were particularly useful in distinguishing between the two compounds as the cis isomer had two medium intensity absorptions at 710 and 735 cm^{-1} while the trans isomer had strong absorptions at 975 and 990 cm^{-1}. Similar cis–trans isomerizations have been noted upon irradiation of *cis*-4-cyclooctenone[13] and *cis*-5-cyclodecenone.[14] Carlson reported[15] the formation of both **10** and **11** upon irradiation of 2-cyclopropylcyclohexanone. Compounds **10** and **11** can be separated by column chromatography using silica gel impregnated with silver nitrate[15] or by gas chromatography (gc) and thus the partial hydrogenation–photoisomerization approach provides a facile route to both of these medium ring enones from **1**.



10 **11**

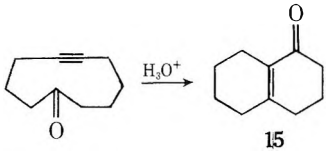
A particularly striking feature of the mass spectra of **10** and **11** is the high intensity of the M − H_2O peak (>90% of the base peak while in cyclononanone this peak is <10% of the base peak). A number of mechanisms could be proposed to account for the enhanced M − H_2O peak but it must be related to the fact that the hydrogens γ to the keto group are allylic and thus abstraction of these by the carbonyl oxygen would be a lower energy process than in the case of cyclononanone. A Dreiding model of the cis enone (**10**) shows that the carbonyl oxygen can come closer than 1.8 Å to these γ hydrogens and so hydrogen abstraction processes such as the McLafferty rearrangement should be possible.[16] In the trans isomer (**11**) this oxygen–γ-hydrogen distance is greater than 1.8 Å but the similarity of the mass spectra of the two isomers (see Experimental Section) suggests that there may be significant isomerization of **11** to **10** upon introduction into the spectrometer. Deuterium labeling experiments would obviously be necessary to gain further insight into the mechanism of these transformations.

Diels–Alder adducts are obtained upon reaction of either alkene[17] or alkyne[18] dienophiles with 2,5-dimethyl-3,4-diphenylcyclopentadienone (**12**).[19] In the alkyne reactions the adduct normally loses a molecule of carbon monoxide to give a substituted *o*-terphenyl system. Reaction of **1** with **12** in refluxing toluene gave adduct **13** in 42% yield. The novel aromatic ketone exhibited only one methyl resonance (τ 8.0) in its nmr spectrum, consistent with the symmetrical nature of the molecule. Formation of **13** is further evidence for the presence of an alkyne linkage in **1**. Dreiding models suggested there might be a possibility of an electronic interaction between the fully substituted benzene ring of the *o*-terphenyl system and the carbonyl group (or an appropriate derivative). The 2,4-dinitrophenylhydrazone (2,4-DNP) of **13** was prepared and its visible spectrum compared with that of the 2,4-DNP of cyclononanone.[20] No difference in the 300–500-nm region of the two spectra was noted and thus there was no indication of an intramolecular charge-transfer interaction between the hexasubstituted benzene ring (donor) and the dinitrosubstituted ring (acceptor).



12 **13**

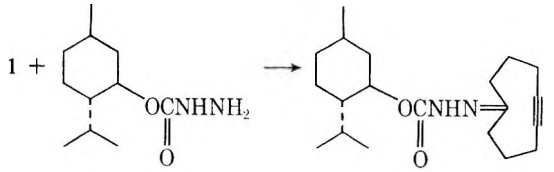
Two different investigations[21,22] showed that 5-cyclodecynone (**14**) underwent acid-catalyzed transannular cyclization to give bicyclo[4.4.0]-1(6)-decen-2-one (**15**) as the



14 **15**

only product. In the present case, treatment of **1** with dilute acid (2 *N* H_2SO_4) in aqueous ethanol gave cleanly the bicyclic ketone **5**. Presumably the mechanism for this cyclization *via* the vinyl cation is the same as that previously outlined for the conversion **14** → **15**.[21] Thus the same type of transannular reaction that was observed with the C_{10} 5-cycloalkynone occurs just as effectively with the C_9 homolog.

A Dreiding model of 5-cyclononynone (**1**) can be assembled but it is quite rigid with the carbonyl oxygen pointing in toward the center of the ring and either above or below the plane created by the triple bond and its adjacent carbon atoms. By preparing an appropriate optically active carbonyl derivative we postulated that it might be possible to separate the two diastereomers formed as a consequence of this rigidity or restricted rotation.[23] Toward this end, **1** was reacted with *l*-menthydrazide (**16**), an optically active reagent for carbonyl compounds developed by Woodward,[24] to give the *l*-menthydrazone (**17**),[25] $[\alpha]_D$ −42.2°. All attempts to separate the two proposed isomers either by tlc or fractional crystallization were unsuccessful. Apparently rotation in the ring is not restricted to the extent that it prevents interconversion between the two isomers. The nmr spectrum of **17** was determined at −50° to slow or stop this interconversion and the sharp methyl doublets of the methyl ring were examined. Again there was no indication of the existence of two compounds either because the interconversion is still too rapid or the chemical shifts of the methyl groups in the two compounds are not sufficiently different.[26]



16 **17**

In conclusion, we have outlined in this report an effective synthesis of 5-cyclononynone (1) from readily available starting materials and have described a number of reactions which support the proposed structure of 1 and also provide easy access to a number of novel medium ring structures.

Experimental Section

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Model IR-5A infrared spectrophotometer, ultraviolet spectra on a Unicam SP 800 spectrophotometer, and mass spectra on a Varian Mat CH7 spectrometer operating at 70 eV. Nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrometer using the internal standard tetramethylsilane (TMS, τ 10.0) and the following designations are used: s = singlet, d = doublet, and m = multiplet. Gas chromatographic (gc) analyses and collections were carried out on an Aerograph Autoprep Model A-700 using either of the following: column A, 20% Carbowax 20M on Chromosorb W, 60–80 mesh, 6 ft × 0.25 in.; column B, 20% OV-210 silicone fluid on Chromosorb W high performance, 80–100 mesh, 5 ft × 0.25 in. Peak areas were determined by triangulation and were not corrected for differences in thermal response. Thin-layer chromatography, tlc, and preparative-layer chromatography, plc, employed silica gel GF 254 in thicknesses of 0.25 and 0.75 mm, respectively. The solvent system used throughout was 1% ethyl acetate–chloroform. Optical rotations were determined at 25° on a Bendix-NPL Automatic Polarimeter, Type 143, using a 1-cm cell and absolute ethanol as solvent. Photochemical irradiations were performed in a Rayonet Model RPR 208 preparative reactor equipped with 300-nm lamps. Elemental analyses were performed by H. S. McKinnon, Chemistry Department, University of Guelph or A. B. Gygli, Microanalysis Laboratory, Toronto.

Preparation of Bicyclo[4.3.0]-1(6)-nonen-2-one (5). A suspension of 8.0 g (66 mmol) of 4,5,6,7-tetrahydroindan (**2**)[4] in 60 ml of absolute methanol was stirred rapidly at −70° while a stream of ozone from a Welsbach generator (200 W) was bubbled through the reaction for 30 min. The suspension had cleared and the characteristic blue color of excess ozone was evident. A solution of 5 g of potassium iodide in 20 ml of water was added to destroy the peroxide formed in the hydrolysis and the reaction was allowed to warm to room temperature at which time the iodine color was discharged with a solution of sodium thiosulfate. To this crude ozonolysis mixture was added 6 g of sodium carbonate and sufficient water to give a total of 60 ml of water added overall. The reaction solution was heated to reflux for 1.5 hr, cooled, and extracted with chloroform. The organic phase was washed with water and brine and dried ($MgSO_4$). Removal of the solvent and distillation gave 4.48 g (50%) of **5** as a colorless liquid which was >95% pure by gc analysis (column B, 170°): bp 49–52° (0.3 mm); ir (neat) 1665, 1640 cm^{-1};[8] uv λ_{max} (EtOH) 250 nm (ϵ 10,600);[8,9] 2,4-DNP derivative, mp 247–247.5 (lit.[8] mp 250°).

The *l*-menthydrazone of **5**[27] was prepared using the general procedure previously described[24] with a reflux period of 7 hr to give pale yellow needles from aqueous ethanol: mp 158–158.5°, uv λ_{max} (EtOH) 268 (ϵ 26,000); $[\alpha]D$ −48.6° (c 1.23).

Preparation of 10-Oxatricyclo[4.3.1.0]-2-decanone (6). To a stirred solution of 9.8 g (72 mmol) of **5** in 22 ml of 30% hydrogen peroxide and 70 ml of methanol at 15° was added dropwise over a period of 15 min a solution of 2.1 g of potassium hydroxide in 9 ml of water. After stirring at 20–25° for 3 hr the reaction mixture was poured into 150 ml of brine and this aqueous phase was extracted with ether. The organic phase was washed with brine and dried ($MgSO_4$). Removal of the solvent and distillation gave 7.75 g (71%) of **6** which exhibited only one peak on gc analysis (column A, 182°): bp 61–65° (0.6 mm); ir (neat) 2920, 1700, 1370, 1090, 915, 880. 790 cm^{-1}; nmr (CCl_4) τ 7.4–8.7 (m). *Anal.* Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found C, 71.20; H, 8.22.

Preparation of 5-Cyclononynone (1). To a solution of 6.88 g (45.2 mmol) of **6** in 75 ml of glacial acetic acid and 75 ml of methylene chloride at −20° was added 8.48 g (45.5 mmol) of *p*-toluenesulfonylhydrazine. The solution was stirred for 0.5 hr at this temperature during which time a white precipitate formed. The reaction was stirred at 0° for 2 hr then at room temperature for 3 hr to give a clear yellow solution. Solid sodium carbonate was added to neutralize the acetic acid and water was added to dissolve any solid present. To two phases were separated and the aqueous phase was extracted with methylene chloride. The combined organic phases were washed with saturated sodium bicarbonate solution and brine and dried ($MgSO_4$). Removal of the solvent and distillation yielded 3.44 g (56%)[28] of **1** which gc analysis (column A, 182°) showed to be >95% pure: bp 46–48° (0.2 mm); ir (neat) 2930, 1695, 1430, 1340, 1190, 1095 cm^{-1}; nmr (CCl_4) τ 7.5–8.1 (m); mass spectrum *m/e* (rel intensity) 136 (18, M^+), 135 (19), 108 (47), 79 (100).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.32; H, 8.89.

The *l*-menthydrazone of **1**[27] was prepared using the general procedure previously described[24] with a reflux period of 40 hr to yield colorless needles from aqueous methanol: mp 167–167.5°; uv λ_{max} (EtOH) 232 (ϵ 10,100); nmr ($CDCl_3$) τ 9.18 (3 H, d), 9.12 (6H, d, J = 5.5 Hz), 7.4–9.3 (21 H, m), 5.3 (1 H, m), 2.5 (1 H, broad s); $[\alpha]D$ −42.2° (c 1.19). All attempts to isolate another derivative from the mother liquors or to separate this product into two compounds by fractional crystallization with aqueous methanol or aqueous ethanol or by tlc failed.

Hydrogenation of 1. (a) With Pd/C. A suspension of 0.50 g (3.7 mmol) of **1** and 50 mg of 5% Pd on charcoal in 25 ml of ethyl acetate under 1 atm of hydrogen at 25° was stirred vigorously until 185 ml (7.5 mmol) had been consumed and the uptake had ceased. The catalyst was filtered and the solvent was removed leaving 0.48 g of a product which was identical in every respect (gc retention time, ir and mass spectrum) with an authentic sample of cyclononanone.[29]

(b) With Nickel Boride (P2) Catalyst.[12] To a stirred solution of 249 mg (1.0 mmol) of nickel acetate tetrahydrate in 8 ml of 95% ethanol under hydrogen was added a solution of 38 mg (1.0 mmol) of sodium borohydride in 7 ml of 95% ethanol to give a finely divided black catalyst. To this stirred catalyst suspension under 1 atm of hydrogen at 25° was added 0.50 g (3.7 mmol) of **1** in 3 ml of ethanol and the gas uptake was followed. After 1 hr 93 ml (3.8 mmol) of hydrogen had been consumed and the uptake had essentially ceased. The catalyst was filtered and the solvent was removed to give 0.46 g of a colorless liquid. Gc analysis (column A, 170°) indicated 91% of **10** (retention time 3.9 min) and 9% of **1** (retention time 7.5 min). An analytical sample of **10** was isolated by preparative gc: ir (neat) 3010, 2930, 1700, 735, 710 cm^{-1}; nmr (CCl_4) τ 7.5–8.4 (12 H, m), 4.4–4.8 (2 H, m); mass spectrum *m/e* (rel intensity) 138 (14, M^+), 120 (90), 82 (63), 67 (100), 55 (96), 54 (98); uv λ_{max} (EtOH) 219 (ϵ 640), 278 (26). *Anal.* Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.19; H, 10.30.

Formation of 11 by Photoisomerization. A solution of 100 mg (0.74 mmol) of **10** in 10 ml of spectroquality benzene was placed in a Pyrex tube and degassed with dry, oxygen-free nitrogen. The tube was sealed with a serum cap and placed in a water-cooled immersion well and the sample was irradiated with 300-nm lamps. Aliquots were withdrawn every few hours and the extent of photoisomerization was monitored by gc (column A, 148°). After 30 hr irradiation the reaction mixture consisted of 80% of **11** (retention time 7.3 min) and 20% of **10** (retention time 7.8 min) and continued irradiation did not change this ratio. An analytical sample of **11** was isolated by preparative gc: ir (neat) 3010, 2930, 1695, 1125, 990, 975 cm^{-1}; nmr (CCl_4) τ 7.5–8.3 (12 H, m), 4.6–4.9 (2 H, m); mass spectrum *m/e* (rel intensity) 138 (14, M^+), 120 (94), 82 (68), 67 (100), 55 (76), 54 (82); uv λ_{max} (EtOH) 219 (ϵ 560), 278 (28). *Anal.* Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.11; H, 10.17.

Preparation of Adduct 13. A solution of 200 mg (1.47 mmol) of **1** and 382 mg (1.47 mmol) of the dimer of 2,5-dimethyl-3,4-diphenylcyclopentadienone (**12**)[19] in 2.5 ml of toluene was heated to reflux for 16 hr during which time the reddish-orange solution changed to a cloudy yellow mixture.[30] The solvent was removed and the residue was triturated with hot hexane leaving a powdery white solid which was discarded. The hexane solution was reduced to a volume of *ca.* 10 ml and upon cooling gave 225 mg (42%) of crystalline product. Recrystallization from hexane gave colorless needles of adduct **13**: mp 204–205°; ir (CCl_4) 3040, 3020, 2940, 1705, 1600, 1490, 1440, 700 cm^{-1}; nmr (CCl_4) τ 8.0 (6 H, s), 7.5–8.0 (8 H, m), 7.0–7.3 (4 H, m), 2.8–3.3 (10 H, m); uv λ_{max} (EtOH) 218 (sh, ϵ 24,300), 228 (ϵ 25,900); mass spectrum *m/e* (rel intensity) 368 (100, M^+), 335 (63), 297 (37), 283 (30), 269 (32); 2,4-DNP derivative, mp 241–242°.[27] *Anal.* Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66. Found: C, 88.07; H, 7.65.

Acid-Catalyzed Cyclization of 1. A solution of 84 mg (0.62 mmol) of **1** in 1 ml of 4 *N* H_2SO_4 and 1 ml of 95% of ethanol was left at room temperature for 12 hr. The solution was then poured into 5 ml of water and extracted with ether. The organic extract was washed with saturated sodium bicarbonate solution and brine and dried ($MgSO_4$). Removal of the solvent left 80 mg of a yellow

oil which was shown by gc analysis (column B, 176°) to be a mixture of 97% of **5** and 3% of **1**. The identity of the major peak was confirmed by isolation and comparison of its spectral properties with an authentic sample of **5**.

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Registry No.—**1**, 52920-58-8; **2**, 695-90-9; **5**, 22118-01-0; **5** *l*-menthydrazone, 52920-61-3; **5** 2,4-DNPH, 52920-62-4; **6**, 39746-31-1; **10**, 52920-63-5; **11**, 52920-64-6; **12**, 26307-17-5; **13**, 52920-59-9; **13** 2,4-DNPH, 52920-65-7; **17**, 52920-60-2.

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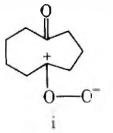

i

prevented the formation of the diperoxide by-product and resulted in an increased yield of **5**. The diperoxide will be the subject of a separate communication.
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(20) Note that in **13** the carbonyl group is part of a nine-membered ring.
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(23) **1** itself has a plane of symmetry and is achiral, but replacement of >C=O by >C=N– introduces the possibility of chirality into the structure *if* the rotation is sufficiently restricted.
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(25) The *l*-menthydrazone of ketone **5** was also prepared for comparison to establish that during the preparation of the derivative of **1** acid-catalyzed cyclization did not occur to ultimately give the derivative of **5** instead.
(26) A referee has suggested that the ready bending of the sp–sp^3 linkage would make **1** considerably less strained than Dreiding models indicate. *e.g.*, E. Kloster-Jensen and J. Wirz, *Angew. Chem., Int. Ed. Engl.* **12**, 671 (1973).
(27) The C, H, and N analysis for this derivative was within the usually acceptable limits of ±0.3%.
(28) If the crude product was purified by silica gel column chromatography, in addition to the isolation of **1** (eluted with 50% ether–petroleum ether), a 20% yield of the tosylhydrazone of **1**,[27] mp 144–145°, was also obtained (eluted with 2% ethyl acetate–ether). Apparently **1** was being formed before the reaction of tosylhydrazine with **6** was complete, but even when the reaction was maintained at 0° overnight before warming to room temperature the yield of **1** was not improved.
(29) Obtained from Aldrich Chemical Co.
(30) The reaction was followed by tlc with adducts **13** and **12** having R_f 0.55 and 0.65, respectively. The crude product could also be purified by plc.

Synthesis and Reactions of 4-Substituted 2-Azaadamantanes

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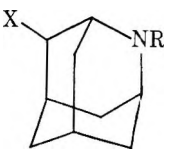
The synthesis of a series of 4-substituted 2-azaadamantyl compounds is reported. The ring system of these compounds was obtained *via* a closure reaction brought about by spontaneous intramolecular opening of an epoxide, at the former double-bond site of N-substituted bicyclo[3.3.1]non-6-en-3-ylamine (**6**), by the amide nitrogen. This unexpectedly facile closure, resulting from the unusual proximity of the amide nitrogen to the back side of the epoxide-bearing ring carbon, is one of several herein described examples of enhanced reactivity at the former double-bond site of this endo-substituted bicyclo[3.3.1]nonane ring system. Acetolysis of the *p*-toluenesulfonate ester of *N*-benzoyl-2-azaadamantan-*anti*-4-ol (**8**) was effected in buffered solution. The only product was anti acetate **14**. Rate measurements demonstrated a slight rate retardation when compared to 2-adamantyl *p*-toluenesulfonate, the analogous carbocyclic system. Attempts to obtain the epimeric syn alcohol **18** by reduction, equilibration, and displacement are described.

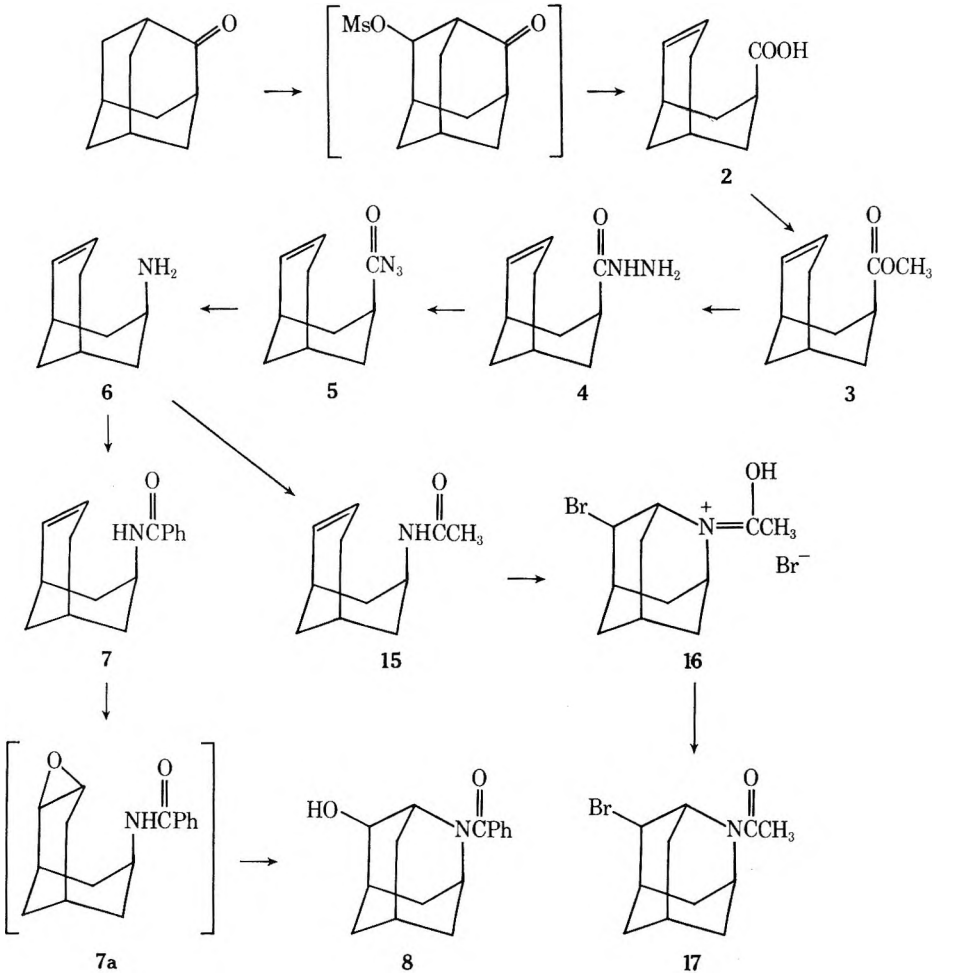
As part of a continuing effort in our laboratories to synthesize hetero analogs of rigid carbocyclic systems[3–5] and in conjunction with our interest in adamantane chemistry,[6–7] we initiated a program of research directed toward the synthesis of adamantyl analogs in which the molecular framework has been altered through replacement of a bridge carbon by a nitrogen. It was our intent, then, to synthesize compounds illustrated by structures **1**. The β-amino and β-amido sulfonate esters could then be subjected to solvolytic conditions to assess the effects of the β nitrogen upon ionization.



1, R = PhCO, $PhCH_2$, H, CH_3; X = OH, OTs

We wish to report here the synthesis of this new class of compounds and our preliminary results on the solvolysis of one of them, *N*-benzoyl-2-azaadamantan-*anti*-4-ol.

Scheme I



Results

N-Benzoyl-2-azaadamantan-*anti*-4-ol (8) was prepared from 2-adamantanone *via* the synthetic route shown in Scheme I. Epoxide **7a** was not obtained upon treatment of olefin **7** with 85% *m*-chloroperbenzoic acid[8] but rather afforded a product which on the basis of its infrared and nmr spectra was assigned ring-closed structure **8**.[9]

Further characterization (Scheme II) of the benzoyl azaadamantanol was accomplished by converting it to its corresponding ketone **9** by the chromium trioxide–pyridine method, and by Jones oxidation. Reduction of the ketone with sodium borohydride returned the starting anti alcohol. Other derivatives, **10–12**, were prepared by conventional synthetic procedures.

It was learned that the 4-substituted 2-azaadamantyl system was also obtainable by reaction of acetamide **15** with bromine in carbon tetrachloride. The reaction procedure yielded a product which was soluble in water and in ethanol, but insoluble in ether and other organic solvents. From its infrared spectrum, it was concluded that the hydrobromide salt of *N*-acetyl-2-azaadamantyl-*anti*-4-bromide (**16**) had been formed. It was not possible to prepare an analytically pure sample, but an elemental analysis did indicate that two bromines were present in the molecule. Neutralization of the salt gave the free bromoacetamide **17**, whose structure was confirmed by infrared, nmr, and elemental analyses.

In contrast to the behavior of the acetamide, addition of bromine to the unprotected amine **6** resulted in precipitation of a bromide salt before reaction could occur at the double bond.

Scheme II

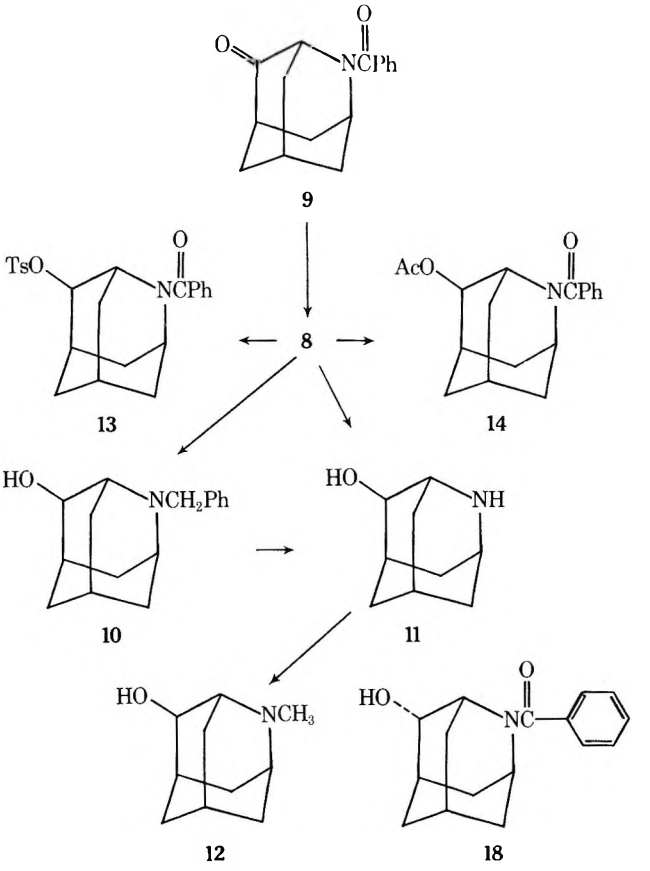


Table I
Acetolyses of *N*-Benzoyl-2-azaadamantan-4-yl *p*-Toluenesulfonate (13) and 2-Adamantyl *p*-Toluenesulfonate

Buffer	*T*, deg	10^5k, sec^{-1}	H^*, kcal	S^*, eu
N-Benzoyl-2-azaadamant-4-yl *p*-Toluenesulfonate (**13**)				
NaOAc (0.01 *M*)	120.0	18.0		
NaOAc (0.01 *M*)	100.0	2.42	29	−2
2-Adamantyl *p*-Toluenesulfonate (**11**)				
KOAc (0.1 *M*)	100.0	10.0		
KOAc (0.1 *M*)	75.15	0.55		
KOAc (0.1 *M*)	25.0	3.25×10^{-4} (calcd)	30	+3

Our synthesis of 4-hydroxy-2-azaadamantane proved to be an uncomplicated procedure due to the ring closure caused by spontaneous intramolecular opening of the epoxide by an amide nitrogen. The anti configuration was assigned assuming conventional back-side attack of the epox the corresponding ketone with sodium borohydride in methanol and sodium borohydride in pyridine returned the anti alcohol. Attempts to equilibrate the alcohols with aluminum *tert*-butoxide, aluminum isopropoxide, and sodium methoxide failed. In another attempt to obtain syn alcohol **18**, a displacement of the *p*-toluenesulfonate group of **13** with sodium acetate was attempted. Hydrolysis of the reaction product gave a material which by infrared, thin layer chromatography, and gc analyses was shown to be the anti alcohol, exclusively.

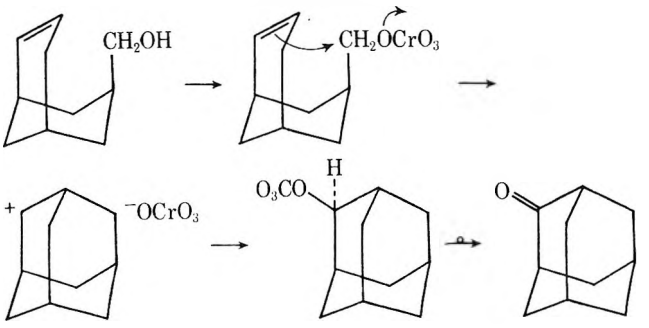
Acetolysis studies of *p*-toluenesulfonate **13** alone were therefore undertaken. Product studies at 100 and 120° in sodium acetate buffered media for a minimum of 8 half-lives revealed anti acetate **14** to be the sole product. The reaction demonstrated linear first-order kinetics at each temperature when kinetic measurements were made. Rates of reaction, which were obtained from the slopes of concentration *vs.* time plots, and are the averages of at least two runs, are given in Table I. Data from similar acetolyses of 2-adamantyl *p*-toluenesulfonate are included for comparison.[10]

Discussion

Our synthesis of 4-hydroxy-2-azaadamantane proved to be an uncomplicated procedure due to the ring closure caused by spontaneous intramolecular opening of the epoxide by an amide nitrogen. The anti configuration was assigned assuming conventional back-side attack of the epoxide. The ease of this closure to the adamantane skeleton, even though initiated by a relatively nonnucleophilic functional group, can be attributed primarily to proximity effects. Indeed, Dreiding models reveal that an atom attached to C_3 of the bicyclo[3.3.1]nonenylmethyl ring system is situated nearly within a C–C bond length of C_7. This certainly explains the similar facile π-route closures to 2-adamantyl derivatives observed by Udding, *et al.*,[11] in treatment of *endo*-bicyclo[3.3.1]non-6-en-3-ylcarbinol with dilute sulfuric acid, and by Schleyer, *et al.*,[12] in the solvolysis of *endo*-bicyclo[3.3.1]non-6-en-3-ylmethyl *p*-toluenesulfonate in aqueous acetone. A related unusual π-route closure was realized in our laboratories[13] from an attempt to oxidize *endo*-bicyclo[3.3.1]non-6-en-3-ylcarbinol to the corresponding carboxaldehyde. The only product obtained was 2-adamantanone, which presumably arose from the route shown in Scheme III.

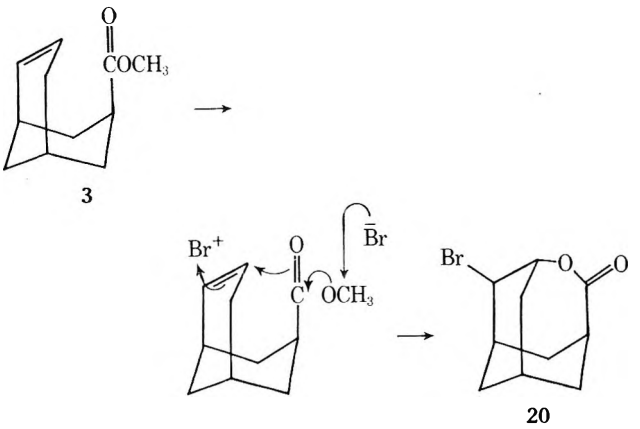
Clearly, the amide-initiated ring closure which we observed was caused by a charge distribution which is nearly

Scheme III



the reverse of these cases. For *endo*-3-*N*-benzamidobicyclo[3.3.1]non-6-ene (**7**), it is likely that any perturbation of the double bond by electrophilic reagents resulting in formation of partial positive charges at C_6 and C_7 can be satisfied at C_7 by orbital overlap with the amido group. Epoxidation of the double bond, or addition of bromine, thus results in the spontaneous ring closures observed.

For similar reasons, addition of bromine to *endo*-bicyclo[3.3.1]non-6-ene-3-carboxylic acid (**2**) results in formation of bromo lactone **20**. While this does not appear to be



3 20

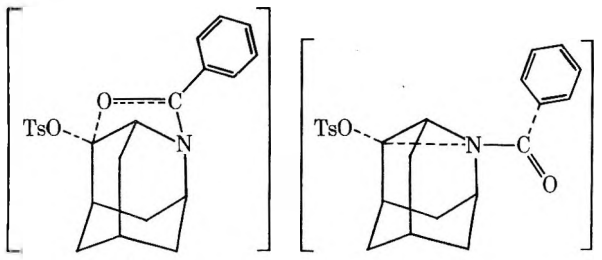
an unusual reaction, isolation of the same lactone from the addition of bromine to methyl ester **3** indicates that the carbonyl oxygen may be capable of effecting the ring closure in these cases.

Our failure, to date, to obtain the syn epimer of **8** precludes a definitive discussion of the solvolytic behavior of the 2-azaadant-4-yl cation. Yet, several points should be made. The production of only anti alcohol **8** from sodium borohydride reduction of ketone **9** seems to indicate a comparatively large steric hindrance at the anti face of the carbonyl. Still, it is possible that this stereospecificity and the failure of aluminum *tert*-butoxide and aluminum isopropoxide to effect what would seem, on this basis, to be a favorable equilibration to syn alcohol are due to complexation of the metallic reagents with the amide group, thus only allowing hydride delivery from the syn face, or to extreme steric factors, since the transition state for the reduction phase of equilibration requires that the hydride donor approach the most hindered face of the carbonyl if it is to produce syn alcohol. The failure of attempted SN2 displacement of the anti *p*-toluenesulfonate with acetate ion must be attributed either to strong steric hindrance to departure of the leaving group, repulsion of the nucleophile by the amide group, or to participation by the amide group in ionization of the ester.

The latter possibility seems the likely explanation for the stereochemical retention during acetolysis despite the fact that the rate at 100° was only one-fourth that of 2-adamantyl *p*-toluenesulfonate at the same temperature. A cal-

culation[14] of the C_3–C_4–C_5 bond angle (111.4°) in the carbonium ion from **13**, based on the position of the principal carbonyl infrared stretching frequency of ketone **9** at 1729.6 cm^{-1}, indicated only a slight difference from the corresponding angle (112.5°) of 2-adamantanone. The small increase in ring strain brought about by the amide nitrogen should thus alter the reactivity of the *p*-toluenesulfonate group of **13** only slightly in the adverse direction.[15]

It seems likely that participation by the amide in stabilizing the carbonium ion may govern the stereochemistry of the product. The precise manner of charge delocalization is not clear as two modes of amide participation appear possible. If the amide is oriented as shown in **21**, 1,3 participation *via* an oxazolinium type intermediate may occur. Otherwise, the amido nitrogen may participate in the manner represented by **22**. Molecular models do not indicate that



21 22

either arrangement is preferred, and either type of assistance would seem to involve introduction of strain in the rigid ring system.

Two rate-influencing effects may be concomitantly operative in solvolytic reactions of **13**: assistance to ionization by the amide, and retardation due to inductive and added ring strain effects of the amide. Unfortunately, our inability to obtain and solvolyze the epimeric syn alcohol complicates our assessment of the effects of the β-amido group. From data reported for the acetolyses of 2-cyclohexyl tosylates, one can estimate a 14-fold rate-retarding inductive effect for the β-benzamido group.[24] Since this leads to a predicted rate considerably smaller than the fourfold retarded rate which we observed, assistance to ionization may in fact be implicated.

Support for this assumption should become possible when other β-amido *p*-toluenesulfonates of this series and others, which have been recently prepared in our laboratories, are studied.

Experimental Section[16]

endo-**Bicyclo[3.3.1]non-6-ene-3-carboxylic acid (2)** was prepared by a modification of the method of Sasaki, *et al.*[17] To a stirred solution of 48.0 g (0.32 mol) of 2-adamantanone in 300 g of 99% methanesulfonic acid was added portionwise over 2 hr 21.6 g (0.336 mol) of sodium azide. The temperature was maintained at 20–25° during the addition. Nitrogen evolution ceased 2 hr after the addition was completed. After stirring an additional hour at room temperature, the reaction solution was diluted with 100 ml of water. An excess of 50% potassium hydroxide solution was carefully[18] added portionwise without external cooling. The exothermic reaction yielded a solution which was extracted once with ether. The aqueous layer was acidified with concentrated hydrochloric acid. The precipitated organic acid was collected by filtration, washed with five 50-ml portions of distilled water, and then dried in a vacuum desiccator over phosphorus pentoxide to give 39.4 g (74%) of **2**, mp 196–198° (lit. mp 195–198°).

Methyl *endo*-Bicyclo[3.3.1]non-6-ene-3-carboxylate (3). To a solution of 16.6 g (0.1 mol) of acid **2** in 200 ml of ether was added portionwise a cold ethereal solution of diazomethane, prepared from 36.3 g of Diazald.[19] Addition of diazomethane was stopped when nitrogen evolution ceased and the yellow color of diazomethane persisted in the reaction solution. The solution was then washed with saturated sodium bicarbonate solution, dried, and concentrated. The methyl ester was obtained as a colorless oil in quantitative yield and was not further purified. Infrared spectrum (film) 3025, 2930, 1730, 1460, 1440, 1360, 1220, 1200, 1100, 1020, and 780 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.30–2.70 (11 H, m), 3.56 (3 H, s), 5.55 (2 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 180 (10), 149 (11), 148 (60), 121 (10), 120 (10), 93, (11), 92 (10), 91 (17), 87 (11), 80 (12), 79 (100), 78 (70), 67 (12), 44 (42), 31 (23), 39 (12).

endo-**Bicyclo[3.3.1]non-6-ene-3-carboxyhydrazide (4).** A solution of 18 g (0.1 mol) of methyl ester **3** in 40 ml of ethanol was heated to reflux with 15 g (0.3 mol) of 99% hydrazine hydrate. After 96 hr, 60 ml of water was added to the reaction solution. A distillation head was attached to the reaction flask and the solution was distilled at atmospheric pressure until the distillation temperature reached 100°. The residue was cooled and stored at 5° overnight. On standing, the oil which had separated from the aqueous solution crystallized. The colorless solid was collected on a filter, washed with water, and dried in a vacuum desiccator over phosphorous pentoxide to afford 15.1 g (84%) of **4**. An analytical sample was prepared by recrystallization from methylene chloride–hexane, mp 113.5–115.5°. Infrared spectrum (mull): 3300, 3200, 3000, 2850, 1630, 1500, 1465, and 725 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.50–2.68 (11 H, m), 3.82 (2 H, m), 7.36 (1 H, br, s).

Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.55. Found: C, 66.76; H, 8.95; N, 15.66.

endo-**Bicyclo[3.3.1]non-6-en-3-ylamine (6).** An aqueous solution of the hydrochloride salt of hydrazide **4** was prepared by warming 14.4 g (0.08 mol) of the hydrazide in 150 ml of water to which 7 ml (0.08 mol) of concentrated hydrochloric acid had been added. Insoluble material was removed by filtration and the aqueous solution was chilled to 0° in an ice–salt bath and 60 ml of carbon tetrachloride was added. A solution of 5.52 g (0.08 mol) of sodium nitrite in 20 ml of water was then added dropwise to the chilled hydrazide hydrochloride solution while rigorously swirling the resultant mixture. When the addition was complete, the mixture was poured into a chilled separatory funnel and the yellow-green organic layer, containing acyl azide **5**, was drawn off into a round-bottom flask containing 100 ml of water and 7 ml of concentrated hydrochloric acid. The mixture was stirred magnetically and allowed to warm until nitrogen evolution commenced. The mixture was then heated to reflux. After 56 hr, the mixture was cooled and the organic layer was separated and dried and concentrated to recover 3 g of a mixture of starting material and acid **2**. The aqueous layer was made strongly basic with solid potassium hydroxide, saturated with sodium chloride, and extracted with methylene chloride. The organic layer was washed once with water, dried, and concentrated to give 7.1 g of crude **6** as a pale brown solid. The crude product was sublimed at 70° (0.2 mm Hg) to give 5.7 g (55%) of air-sensitive pure amine as a colorless wax. Infrared spectrum (mull): 3350, 3150, 2925, 1580, 1435, 1270, 1070, 920, 900, and 860 cm^{-1}.

The amine was converted to its hydrochloride salt by dissolving 0.8 g (5.8 mmol) of **6** in 30 ml of solution of methylene chloride–ether (1:2) and bubbling dry hydrogen chloride gas through the resultant solution until no further precipitation of salt was observed. The precipitate was collected on a filter, washed with ether, and recrystallized from 2-propanol–ether, mp > 300°.

Anal. Calcd for $C_9H_{15}N \cdot HCl$: C, 62.23; H, 9.29; N, 8.07. Found: C, 61.98; H, 8.99; N, 7.89.

endo-**Bicyclo[3.3.1]non-6-en-3-ylbenzamide (7).** To a solution of 7.2 g (0.053 mol) of amine **6** in 35 ml of benzene containing 4.2 g (0.053 mol) of pyridine was added dropwise 7.45 g (0.053 mol) of benzoyl chloride. The temperature was maintained at 20–25° during the addition. The solution became yellow and a precipitate formed. When the addition was complete, the reaction mixture was stored overnight at 5°, then washed with six 25-ml portions of water, dried, and concentrated to 12.5 g of a slightly yellow oil. Trituration with *n*-hexane gave 11.5 g (85%) of **7** as a white crystalline solid. An analytical sample was obtained by recrystallization from ether–pentane, mp 83–85°. Infrared spectrum (mull); 3350, 3055, 2850, 2025, 1630, 1600, 1580, 1530, 1485, 1350, 1300, 715, and 700 cm^{-1}; nmr ($NCDCl_3$) (TMS) δ 1.34–2.70 (10 H, m), 4.50 (1 H, m), 5.70–6.40 (2 H, m), 7.20–7.80 (6 H, m).

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.62; H, 7.94 N, 5.80. Found: C, 79.81; H, 8.11 N, 5.76.

N-**Benzoyl-2-azaadamantan-*anti*-4-ol (8).** To 4.04 g (0.02 mol) of 85% *m*-chloroperbenzoic acid dissolved in 40 ml of methylene chloride was added dropwise a solution of 4.8 g (0.02 mol) of **7** dissolved in 40 ml of methylene chloride. The temperature was maintained below 25° during the addition. Afterward, the solution was allowed to stir at room temperature for 18 hr. The excess oxidizing agent was destroyed by washing with 10% sodium bisulfite

solution and the resulting solution was washed successively with saturated sodium bicarbonate solution and water until neutral. The solution was dried and concentrated to give 5.1 g of a colorless oil which crystallized upon treatment with a single drop of ethanol. The resultant oily solid was slurried with hexane and filtered to give 4.2 g (82.5%) of **8** as a white crystalline solid. An analytical sample was prepared by recrystallization from benzene–hexane, mp 143–145°. Infrared spectrum ($CHCl_3$): 3320, 2930, 2850, 1590, 1570, 1445, 1375, 1080, 1025, 970, 920, 790, 735, and 700 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.18–2.54 (10 H, m), 3.45 (1 H, s), 3.80 (2 H, m), 4.75 (1 H, m), 7.34 (5 H, s).

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.85; H, 7.29; N, 5.46.

***N*-Benzyl-2-azaadamantan-*anti*-4-ol (10).** Reduction of amide **8** was effected using the method of Brown and Heim.[20] A 2.57-g (0.01 mol) sample of **8** in 25 ml of tetrahydrofuran was reacted with 20 ml of an approximately 1 *M* solution of diborane in tetrahydrofuran. After heating at reflux for 3 hr, the reaction was cooled in an ice bath and 10 ml of 6 *N* hydrochloric acid was added. When hydrogen evolution had ceased, the tetrahydrofuran was distilled off and the precipitated boric acid was removed by filtration. The resultant aqueous solution was saturated with sodium hydroxide and extracted with ether. The ether extract was washed with water, dried, and concentrated to give 2.3 g (90%) of **10** as a white crystalline solid. An analytical sample was prepared by recrystallization from cyclohexane–pentane, mp 94.5–96°. Infrared spectrum (mull): 3340, 2930, 2850, 1500, 1455, 1360, 1150, 1080, 1035, 1000, 740, and 700 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.18–2.33 (11 H, m), 2.67 (2 H, m), 3.81 (2 H, s), 4.00 (1 H, m), 7.24 (5 H, br, s).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.69; H, 8.58; N, 5.61.

2-Azaadamantan-*anti*-4-ol (11) was prepared by hydrogenolysis of an ethanolic solution of 0.73 g (0.003 mol) of benzylamine **10** employing 100 mg of 5% palladium on carbon as catalyst. When the theoretical amount of hydrogen had been absorbed, the reaction mixture was filtered and concentrated to obtain 0.42 g (78%) of **11** as a white solid. The hydrogen oxalate salt was prepared by dissolving the free amine in ethanol, adding an equivalent of oxalic acid dissolved in ethanol and effecting precipitation of the resultant salt with ether. Recrystallization from 2-propanol–ether gave analytically pure material, mp 172–175° dec. Infrared spectrum (mull): 3500–3100, 2900, 2850, 1640, 1580, 1460, 1060, and 1025 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO \cdot C_2H_2O_4$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.49; H, 6.55; N, 5.94.

***N*-Methyl-2-azaadamantan-*anti*-4-ol (12).** To a solution of 1.1 g of **11** (7.2 mmol) in 10.8 g (36 mmol) of 90% formic acid was added 0.8 g (8 mmol) of 30% formaldehyde. The resultant solution was heated to reflux. After 12 hr, the solution was cooled, 10 ml of water was added, and the excess formic acid was destroyed using solid sodium carbonate. The mixture was then extracted with ether and the ether solution was washed with water, dried, and concentrated to give 1.1 g (90%) of **12** as a white solid, mp 164–165°. Infrared spectrum (mull): 3120, 2920, 2850, 1470, 1380, 1305, 1120, 1025, 1010, and 785 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.20–2.38 (10 H, m), 2.57 (3 H, s), 2.62 (2 H, m), 3.08 (1 H, s), 4.10 (1 H, m).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.65; H, 10.53; N, 8.29.

***N*-Benzoyl-4-oxo-2-azaadamantanone (9).** Alcohol **8** was oxidized to the corresponding ketone **9** by a Sarett (A)[21] and a Jones (B)[22] oxidation procedure.

Method A. To a solution of 1.9 g (0.024 mol) of dry pyridine in 30 ml of methylene chloride was added 1.2 g (0.012 mol) of chromium trioxide. The purple solution was stirred for 15 min. A solution of 0.514 g (0.002 mol) of **8** in 10 ml of methylene chloride was added in one portion to the stirring chromium trioxide–dipyridine solution. A black, tarry precipitate separated immediately. The mixture was stirred for 30 min, then the supernatant liquid was decanted and the residue rinsed with ether. The organic solutions were combined, washed with 5% aqueous sodium hydroxide solution, 5% hydrochloric acid, and finally with water. The solution was dried and concentrated to give 0.465 g (90%) of **9** as a pale yellow oil.

Method B. The Jones reagent was prepared by dissolving 6.7 g of chromium trioxide in 12.5 ml of water and adding 5.8 ml of concentrated sulfuric acid. Precipitated salts were dissolved by adding a minimal amount of water. To a solution of 0.514 g (0.002 mol) of **8** in 10 ml of acetone the oxidizing solution was added dropwise until its characteristic orange color persisted in the reaction flask. The temperature during the addition was maintained below 35°. The solution was decanted from the precipitated green chromium salts, and the residue was then washed with acetone. The combined organic solutions were treated with a few additional drops of oxidizing agent. Excess oxidizing agent was destroyed with isopropanol and then the acidic solution was neutralized with solid bicarbonate, filtered, and concentrated to remove acetone. The aqueous solution was saturated with sodium chloride and extracted with ether. The extracts were dried and concentrated to afford 0.492 g (95%) of **9** as a colorless oil.

The products of methods A and B were identical. Infrared spectrum (film): 3050, 2925, 2860, 1730, 1620, 1575, 1450, 1410, 1345, 1310, 1245, 1095, 1075, 1055, 1030, 975, 790, 720, and 700 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.77–2.50 (10 H, m), 2.75 (1 H, m), 4.50 (1 H, v br s), 7.40 (5 H, s).

***N*-Benzoyl-2-azaadamant-*anti*-4-yl *p*-Toluenesulfonate (13).** To a solution of 2.57 g (0.01 mol) of alcohol **8** in 20 ml of dry pyridine was added 1.91 g (0.01 mol) of freshly purified *p*-toluenesulfonyl chloride.[23] The reaction temperature was maintained at 5° for 14 days. The solution, which had deposited crystals of pyridine hydrochloride, was poured into ice–water and extracted with methylene chloride. The methylene chloride extracts were successively washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, and water. The extracts were dried and concentrated to give 3.2 g (80%) of **13** as a colorless oil which crystallized on standing at 0°. Recrystallization from ether–pentane gave an analytical sample, mp 100.5–102.5°. Infrared spectrum (mull): 3010, 2940, 2880, 1640, 1595, 1460, 1420, 1375, 1360, 1290, 1185, 1170, 980, 960, 860, 810, 720, and 700 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.40–2.40 (10 H, m), 2.47 (3 H, s), 3.90 (1 H, m), 4.68 (2 H, m), 710–800 (9 H, m).

Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.29; H, 5.89; N, 3.41; S, 7.81. Found: C, 67.01; H, 6.12; N, 3.59; S, 7.55.

***N*-Benzoyl-2-azaadamant-4-yl Acetate (14).** To a solution of 0.79 g (1 mmol) of pyridine in 10 ml of acetic anhydride was added 0.257 g (1 mmol) of alcohol **8**. The temperature was maintained at 10° during the addition. The reaction solution was stored at 5° overnight, treated with 25 ml of saturated sodium acetate solution, washed with saturated sodium bicarbonate solution and water, dried, and concentrated. Acetate **14** was obtained as a colorless oil in 85% yield. Infrared spectrum (film): 3050, 2940, 2860, 1735, 1640, 1440, 1420, 1370, 1300, 1240, 1200, 1090, 1040, 1035, 1000, 975, 780, 740, and 700 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.40–2.40 (10 H, m), 2.00 (3 H, s), 3.90 (1 H, br m), 4.40 (1 H, m), 4.98 (1 H, br m), 7.46 (5 H, br s).

***N*-Acetyl-*endo*-bicyclo[3.3.1]non-6-en-3-ylamine (15).** To a solution of 2.37 g (0.03 mol) of dry pyridine in 25 ml of acetic anhydride was added 4.1 g (0.03 mol) of freshly sublimed amine (**6**). The temperature was maintained at 5° for 12 hr. The solution was then treated as in the preparation of acetate **14** to obtain 4.6 g (85%) of **15** as a white crystalline solid, mp 94–96°. An analytical sample was recrystallized from ether–pentane. Infrared spectrum (mull): 3340, 3015, 2910, 2850, 1640, 1510, 1460, 1380, 1290, 760, 730, and 690 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.40–2.55 (13 H, m), 4.26 (1 H, m), 5.75–6.33 (2 H, m), and 6.40–7.05 (1 H, br m).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.82. Found: C, 73.65; H, 9.37; N, 7.61.

***N*-Acetyl-2-azaadamant-4-yl Bromide (17).** To a solution of 1 g (5.57 mmol) of **15** in 15 ml of carbon tetrachloride was added dropwise a 5% solution of bromine in carbon tetrachloride until the color of bromine persisted in the reaction mixture. Decolorization was slow and a gummy orange precipitate formed. When the addition was complete, the solvent was evaporated under a stream of nitrogen. The residue was triturated with ether to give an off-white solid. This hydrobromide salt **16** was recrystallized from ethanol–ether, mp 173–177° dec. Infrared spectrum (mull): 2925, 2850, 2425, 1650 (weak, broad), 1460, 1410, 1080, and 755 cm^{-1}.

The salt was dissolved in water, neutralized with sodium bicarbonate solution, extracted with ether, dried, and concentrated to give 1.0 g (70%) of **17** as a white solid. Sublimation at 70° (0.5 mm) afforded an analytical sample, mp 83–85°. Infrared spectrum (mull): 2930, 2850, 1650, 1470, 1450, 1440, 1420, 1360, 1310, 1220, 1105, 1095, 970, and 750 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.46–2.75 (10 H, m), 2.10 (3 H, s), 4.05 (1 H, m), 4.45 (1 H, m) 4.93 (1 H, m).

Anal. Calcd for $C_{11}H_{16}BrNO$: C, 51.17; H, 6.25; Br, 30.96. Found: C, 51.17; H, 6.26; Br, 31.23.

2-Bromo-4-oxa-5-oxohomoadamantane (20). Method A. To 1 g (6 mmol) of carboxylic acid **2** in 20 ml of carbon tetrachloride was added dropwise a 5% solution of bromine in carbon tetrachloride until the characteristic orange-yellow color of bromine persisted.

During the addition, decolorization was rapid and a precipitate formed. The precipitate was collected by filtration to obtain 1.1 g (80%) of **20** as a white solid, mp 132–134°.

Method B. To 0.5 g (2.8 mmol) of ester **3** in 10 ml of carbon tetrachloride was added a solution of 5% bromine in carbon tetrachloride as above. Work-up as above gave 0.45 g (70%) of **20** as a white crystalline solid. An analytical sample was obtained by recrystallization from cyclohexane, mp 132–134°. Infrared spectrum (mull): 2025, 2855, 1725, 1460, 1395, 1385, 1165, 1100, 1030, 995, 980, 920, and 725 cm^{-1}; nmr ($CDCl_3$) (TMS) δ 1.38–2.92 (10 H, m), 3.12 (1 H, m), 4.33–4.70 (2 H, m).

Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.34; Br, 32.60. Found: C, 49.27; H, 5.29; Br, 32.83.

Reductions of *N*-Benzoyl-4-oxo-2-azaadamantane (9). (A) Sodium Borohydride in Methanol. A solution of 0.255 g (1 mmol) of ketone **9** in 10 ml of methanol was stirred at room temperature while 0.036 g (1.1 mmol) of sodium borohydride in a mixture of 1 ml of water and 5 ml of methanol was added. The solution was stirred for 4 hr. Hydrolysis was effected by the addition of water and 15% potassium hydroxide solution. The solution was diluted with 50 ml of water and extracted with three 15-ml portions of methylene chloride. The combined organic extractions were washed with water, dried, and concentrated to obtain 0.24 g (98%) of a viscous oil which solidified on standing. Infrared and gc analyses revealed the product to be 100% anti alcohol **8**.

(B) Sodium Borohydride in Pyridine. To a solution of 0.255 g (1 mmol) of ketone **9** in 10 ml of dry pyridine, stirring at room temperature, was added 0.108 g (3.4 mmol) of sodium borohydride in 10 ml of pyridine. After 24 hr, the reaction was worked up in the usual manner to obtain 0.216 g (85%) of 100% anti alcohol **8**.

Attempted Equilibrations of *N*-Benzoyl-2-azaadamantan-*anti*-4-ol (8). Method A. A mixture of 0.256 g (1.0 mmol) of anti alcohol **8**, 0.246 g (1.0 mmol) of aluminum *tert*-butoxide, and 0.002 g (0.01 mmol) of fluorenone in 10 ml of benzene was sealed in a tube and heated at 125° for 240 hr. After cooling, the contents of the tube were diluted with 40 ml of methylene chloride and washed with 10% hydrochloric acid until neutral and then with saturated aqueous sodium bicarbonate solution. The organic solution was dried and concentrated to give 0.248 g (98%) of alcohol plus a trace of fluorenone. The mixture was dissolved in the minimum amount of ether and percolated through a silica gel column packed in hexane. Fluorenone eluted rapidly with hexane. The alcohol was eluted with chloroform. Analysis (infrared spectra and gc) revealed that 100% starting anti alcohol was recovered.

Method B. To a solution of 0.256 g (1.0 mmol) anti alcohol 8 in 20 ml of dry 2-propanol[24] was added 0.400 g of freshly distilled aluminum isopropoxide. A 0.1-ml portion of acetone was added and the solution was heated at reflux for 96 hr. The reaction solution was poured into 100 ml of water containing 3 ml of concentrated hydrochloric acid, and the mixture was extracted with ether. The ether solution was washed with water and with saturated sodium bicarbonate solution, dried, and concentrated. Only starting alcohol was recovered.

Method C. To a solution of 0.512 g (2 mmol) of anti alcohol 8 in 25 ml of methanol was added 0.460 g (20 mg-atoms) of sodium in small pieces. A small amount of *N*-benzoyl-4-oxo-2-azaadamantane (**9**) was added and the mixture was heated at reflux for 96 hr under an argon atmosphere. After cooling, the solution was poured into 200 ml of water and extracted with five 50-ml portions of methylene chloride. The combined extracts were washed once with water, dried, and concentrated to give 0.210 g (40%) of an alcohol which upon analysis was shown to be 100% starting material.

Trimethylsilylation of Alcohols 8 and 10. To approximately 10 mg of alcohol in a 1-dram vial equipped with a micro stirring bar was added 1 ml of a silylating mixture composed of one part trimethylsilyl chloride, one part hexamethyldisilizane, and ten parts pyridine. The vial was capped and the mixture was stirred at room temperature overnight. The crude product was poured into 20 ml of water and extracted with three 15-ml portions of ether. The combined extracts were washed once with 10% hydrochloric acid, twice with water, and once with saturated sodium bicarbonate solution. Drying over magnesium sulfate and evaporation of the solvent afforded samples for gc analysis.

Acetolysis Product Studies. Eight Pyrex tubes, each containing 0.0125 g (3.02×10^{-5} mol) of **13** in 5 ml of 0.01 *M* sodium acetate buffered acetic acid containing 1% acetic anhydride, were flushed with nitrogen and sealed. The tubes were heated at constant temperature (100 and 120°) for a minimum of 8 half-lives. Duplicate runs were made for each temperature. After cooling, the contents of the tubes were combined and poured into 160 ml of water and extracted with five 20-ml portions of ether. The combined extracts were washed with water and 5% sodium bicarbonate solution and concentrated. The resulting acetate was compared by infrared spectroscopy and thin layer chromatography to an authentic sample of acetate **14** and was found to be identical. The acetate was then hydrolyzed to its corresponding alcohol by stirring overnight in ethanolic potassium hydroxide. The solution was neutralized with 6 *N* hydrochloric acid, and the ethanol was evaporated. Treatment of the residue with methylene chloride gave a solution which was dried and concentrated to afford a compound which possessed an infrared spectrum and a thin layer chromatogram identical with alcohol **8**. Approximately 5 mg of this alcohol was converted to the corresponding trimethylsilyl ether by the procedure previously described. The remaining alcohol was reduced to the corresponding benzylamino alcohol by the biborane reduction procedure previously described. This amino alcohol was also converted to its trimethylsilyl ether in the usual manner. The silyl ethers were analyzed by gc, using a 50 ft AP-L support coated open tubular (SCOT) capillary column. The following retention times were observed: trimethylsilyl ether of **8**, 235°, pressure 20 psi, retention time 7.2 min; trimethylsilyl ether of **10**, 210°, pressure 10 psi, retention time 7.0 min. In each case there was only one product peak.

Kinetic Studies. J. T. Baker reagent grade glacial acetic acid, to which was added 1% acetic anhydride, was employed in the acetolysis rate determinations. Standard 0.01 *N* perchloric acid in glacial acetic acid was prepared and standardized against potassium hydrogen phthalate. A 0.01 *N* solution of sodium acetate in glacial acetic acid was prepared and standardized against the perchloric acid solution. All titrimetric determinations were made with a 5-ml microburet precise to 0.01 ml using a 0.2% solution of crystal violet in glacial acetic acid as indicator. The end point of each titration was taken as the point at which no violet color was detectable. Constant temperature was maintained with a Neslab TEX 9-H isothermal bath filled with Dow-Corning 200 silicone fluid. Temperatures were determined with a calibrated National Bureau of Standards thermometer.

The general procedure for each kinetic run was as follows. The *p*-toluenesulfonate was weighed into a 50-ml volumetric flask and diluted to volume with standard sodium acetate in glacial acetic acid. Aliquots of this solution were sealed in ampules (Kimble Neutraglas, No. 12012-L) and immersed in the isothermal bath. At appropriate intervals, tubes were withdrawn, cooled in ice–water, and opened, and the contents were titrated with standard perchloric acid. The reaction was followed through approximately 3 half-lives, with zero time taken as the time the tubes were immersed in the bath.

The first-order rate constants were determined by the use of PLSTSQR, a specially written computer program (APL language) which plots at a terminal the graph of ln [ROTS] *vs.* time, then calculates the best rate fit to the valid points by the method of least squares.

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Registry No.—**1**, 700-58-3; **2**, 21932-98-9; **3**, 38773-17-0; **4**, 53092-70-9; **4** HCl, 53092-71-0; **6**, 53092-72-1; **6** HCl, 53092-73-2; **7**, 40923-03-3; **8**, 40810-53-5; **9**, 53092-74-3; **10**, 40810-54-6; **11**, 53092-75-4; **11** oxalate salt, 53154-31-7; **12**, 53092-76-5; **13**, 53092-77-6; **14**, 53092-78-7; **15**, 53092-79-8; **16**, 53092-80-1; **17**, 53092-81-2; **20**, 53152-40-2.

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Studies on 4-Quinazolinones. VII.[1] Some Novel Transformations

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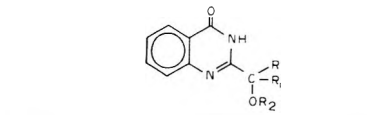
2-(1′-Hydroxydiphenylmethyl)-4-quinazolinone (**1**) or the *O*-acetate (**2**) on refluxing with acetic anhydride and sodium acetate yielded 1,1-diphenyl-3-methylene-9-oxo-9*H*-oxazolo[3,4-*a*]quinazoline (**3**), which gave 1-acetyl-2-(1′-ethoxydiphenylmethyl)-4-quinazolinone (**6**) with ethanolic acetic acid. Both **3** and **6** regenerated the *O*-acetate (**2**) upon treatment with hydrochloric acid. Treatment of **3** or **6** with sodium borohydride in ethanol under reflux furnished 2-methyl-3-(o-hydroxymethylphenyl)-4-imino-5,5-diphenyloxazolidine (**13**) by an unusual amide reduction to a primary alcohol with concomitant hydrogenolytic cleavage of the 3,4-bond of the 4-quinazolinone system. Further hydrogenolysis of **13** in the presence of 10% Pd/C and perchloric acid gave **14**.

In continuation of our investigations of the reactions of 4-quinazolinones[1,3-5] we attempted the acetylation of 2-(1′-hydroxydiphenylmethyl)-4-quinazolinone (**1**)[4] with refluxing acetic anhydride in the presence of fused sodium acetate. The major product obtained was a new compound A, mp 163–164°, in approximately 60% yield in addition to 22% of the desired *O*-acetate **2**. The acetate **2** which also afforded compound A under the same condition was, however, the only isolable product in *ca.* 60% yield when **1** was refluxed with acetic anhydride alone.



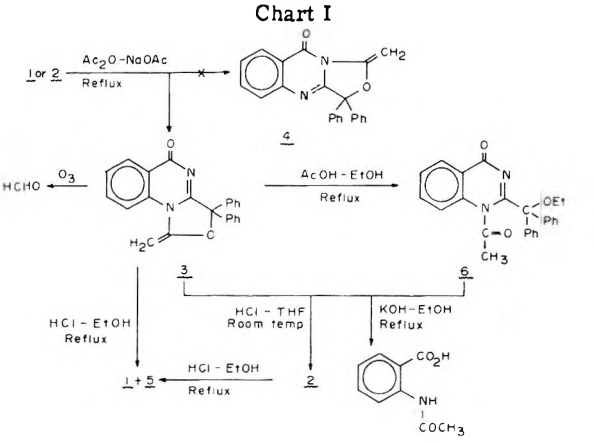
Compound A was analyzed for $C_{23}H_{16}N_2O_2$. Although the mass spectrum did not exhibit the molecular ion, the peak at *m/e* 310 (base peak) in the highest mass region corresponding to $C_{21}H_{14}N_2O$ conceivably could arise by facile expulsion of ketene in the primary fragmentation. The intense bands at 1686, 1694 (sh), 1624, and 1594 cm^{-1} in the ir spectrum (Nujol) indicated the intact 4-quinazolinone moiety in the compound. The nmr spectrum showed a one-proton multiplet at δ 8.46 assignable to an aromatic proton peri to the carbonyl,[6] signals for 13 other aromatic protons, and a pair of sharp doublets at δ 4.67 and 5.6 (J = 3 Hz) attributed to an *exo*-methylene function. This latter assignment was confirmed by the isolation of formaldehyde on ozonolysis.

Treatment of compound A with 1% ethanolic acetic acid at room temperature resulted in recovery of starting material. However, upon refluxing it afforded a product, $C_{25}H_{22}N_2O_3$, mp 158–159°, characterized as 1-acetyl-2-(1′-ethoxydiphenylmethyl)-4-quinazolinone (**6**). The nmr spectrum deserves special mention. Apart from the signals for 14 aromatic protons and a singlet at δ 2.11 for a $-COCH_3$ group, it exhibited a typical ABC_3 pattern composed of a three-proton triplet at δ 1.18 and a centrosymmetric two-proton multiplet around δ 3.38 for the $-O-CH_2-CH_3$ group clearly indicating the $-CH_2-$ protons to be diastereotopic. The first-order analysis of the AB part of the spectrum gave δ_A and δ_B values of 3.51 and 3.26, respectively, and the coupling constants J_{AB} = 9.5 Hz and J_{AC} = J_{BC} = 7 Hz were in excellent agreement with those recorded for the nonequivalent methylene protons of acetaldehyde diethyl acetal.[7] Since the nonequivalence was found to be temperature independent in the range of 30–86° and the corresponding deacetyl derivative (**5**) showed a simple A_2X_3 spectrum, the nonequivalence of the methylene protons presumably results from restricted rotation due to the presence of the acetyl function at N_1 rather than to different populations of the rotamers.[8]

Alkaline hydrolysis of either compound A or **6** with 5% alcoholic KOH furnished *N*-acetylanthranilic acid.

All the above observations (Chart I) appear best explained by the assignment of structure **3** (1,1-diphenyl-3-methylene-9-oxo-9*H*-oxazolo[3,4-*a*]quinazoline) to compound A and not the other possible alternative structure **4**.

Chart I

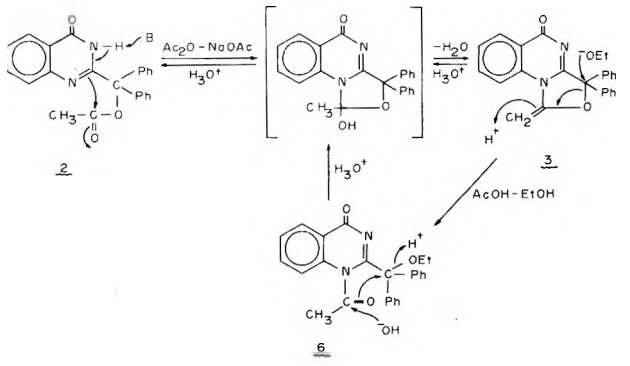


The observed transformation seems to require two phenyl substituents on the same carbon atom to favor cyclization at N-1. Thus, 2-(α-hydroxybenzyl)- and 2-(1′-hydroxyisopropyl)-4-quinazolinones (**7** and **8**) under the specified condition yielded the respective *O*-acetates (**9** and **10**), which regenerated the original alcohols on hydrolysis with dilute ammonia.

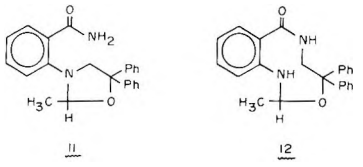
The reverse process was also observed upon treatment of **3** or **6** with dilute acid in THF to afford the *O*-acetate (**2**). On the other hand, hydrolysis of **3** with 5% ethanolic HCl under reflux yielded **1** and a compound, mp 200–202°, for which the nmr and the mass spectral data were in good agreement with 2-(1′-ethoxydiphenylmethyl)-4-quinazolinone (**5**). The apparent intermediacy of the *O*-acetate (**2**) was confirmed by conversion to both **1** and **5** on similar treatment.

The mechanism envisaged for the formations of **3** and **6** from **2** and the reverse process is given in Scheme I.

Scheme I

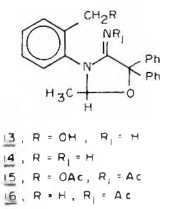


Both **3** and **6** on treatment with $NaBH_4$ in refluxing ethanol afforded compound B, mp 150–151°. It analyzed for $C_{23}H_{22}N_2O_2$ indicating the addition of six hydrogen atoms to **3** during reduction. The presence of a $-CH(CH_3)-O-CPh_2-$ moiety in the compound was revealed by the mass spectrum (high resolution) which showed intense peaks at 210 ($C_{15}H_{14}O$), 209 ($C_{15}H_{13}O$), 166 ($C_{13}H_{10}$), and 165 ($C_{13}H_9$) besides primary loss of CH_3CHO and Ph_2CO. Either structure **11** or **12** was thus considered[10] likely for



compound B, since disubstituted 4-quinazolinones are known[5,9] to undergo reductive ring cleavage at the 1,2- or 2,3-bond on similar treatment with metal hydrides.

Structure **11** was incompatible with the nmr spectrum which was in accord with structures **12** or **13**, since a broad two-proton singlet centered at δ 4.34 converted to a pair of AB doublets at δ 4.3, and δ 4.38 (J = 13 Hz) on deuteration showed the presence of a $-CH_2-$ coupled with a NH or OH proton. That the compound should be represented by the



13, R = OH, R_1 = H
14, R = R_1 = H
15, R = OAc, R_1 = Ac
16, R = H, R_1 = Ac

unexpected structure **13** [2-methyl-3-(o-hydroxymethylphenyl)-4-imino-5,5-diphenyloxazolidine] became apparent from the following evidences: (i) compound B formed an *O,N*-diacetate (**15**), the mass spectrum of which showed a low-intensity peak at M − 73 for a CH_2OAc function; and (ii) on catalytic hydrogenation with 10% Pd/C in the presence of perchloric acid B underwent hydrogenolysis to **14**, $C_{23}H_{22}N_2O$ (M^+ 342), forming a *N*-monoacetate (**16**). The nmr spectrum of **14** exhibited a three-portion singlet for a deshielded $C-CH_3$ group at δ 1.89 at the expense of the signals for $-CH_2OH$. Appearance of a peak at 1345 cm^{-1} in the ir spectrum of **14** also supported the assignment.

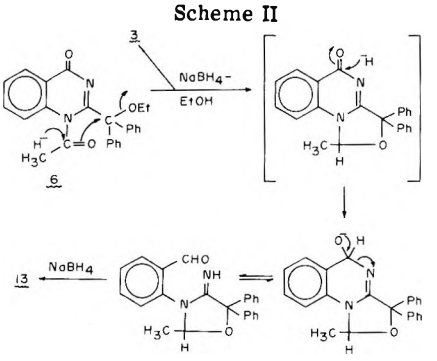
The ir absorption at 1650 cm^{-1} of both **13** and **14** could now be assigned to the C=NH group, the reluctance of which toward further reduction or hydrolysis is probably due to the steric hindrance caused by the vicinal *gem*-diphenyl groups.

Though the reduction of the amide carbonyl, normally resistant to borohydride, to primary alcohol with concomitant hydrogenolytic cleavage of the 3,4-bond of the 4-quinazolinone system is novel, it is not without analogy in the literature. Witkop and his coworkers[11–14] reported the conversion of cyclic imides, *viz.*, succinimide, glutarimides including phthalimidoglutarimides, and 5,6-dihydro-2,4-dioxopyrimidines principally to amido alcohols by the same reagent.

We believe, however, that the observed unusual transformation requires the oxazoloquinazolinone rather than the 4-quinazolinone system itself since 3-phenylquinazol-2,4-dione has been reported[14] to be inert to borohydride reduction and we also did not encounter any such product during our metal hydride reduction studies[5] on variously substituted 4-quinazolinones. Moreover, the same product **13** from both compounds **3** and **6** suggests that the reaction most probably proceeds through a common intermediate.

Thus, the mechanism of the observed transformation is envisaged in Scheme II, the amide reduction being analo-

Scheme II



gous to the one suggested by Witkop, *et al.*[11] Though the intermediate carbinolimine or its ring-chain tautomeric iminoaldehyde was not obtained by us perhaps due to the vigorous conditions used, Kondo and Witkop[14] actually isolated, at least in some cases, the carbinolamide expected in their systems.

Experimental Section[15]

2-(1′-Acetoxydiphenylmethyl)-4-quinazolinone (2) from 1. 2-(1′-Hydroxydiphenylmethyl)-4-quinazolinone[4] (**1**, 0.1 g) was heated on a steam bath with acetic anhydride (1 ml) and pyridine (0.5 ml) for 4 hr. Usual work-up led to quantitative recovery of the starting material.

However, compound **1** (0.1 g) when refluxed with acetic anydride (1 ml) alone for 2 hr afforded a deep-green gum which on repeated crystallizations from benzene and then from ethanol furnished the *O*-acetate (**2**, 65 mg): mp 219–221° dec; ir 1757, 1661, 1642, 1600, and 1210 cm^{-1}.

Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.50; H, 4.90; N, 7.56. Found: C, 74.60; H, 5.03; N, 7.66.

1,1-Diphenyl-3-methylene-9-oxo-9*H*-oxazolo[3,4-*a*]quinazoline (3) from 1. A mixture of compound **1** (4 g), acetic anhydride (20 ml), and anhydrous sodium acetate (2 g) was refluxed for 6 hr. A dark-brown solid was obtained on decomposition of excess reagent with water. It was filtered, dissolved in chloroform (100 ml), washed successively with 5% Na_2CO_3 solution and water, dried, and evaporated. The crude product on crystallization from benzene yielded the major part of *O*-acetate (**2**, 0.75 g), recrystallized from alcohol in transparent plates, mp 219–221° dec.

The mother liquor from the above crystallization was then subjected to column chromatography. Benzene–petroleum ether (1:1, 1.2 l.) eluted **3** (2.5 g, 60%) crystallizing out of alcohol in fine needles: mp 164–165°; ir 1694 sh, 1686, 1623, 1594 cm^{-1}; nmr δ 4.67 and 5.6 (a pair of doublets, 1 H each, $=CH_2$, J_{AB} = 3 Hz), 7.3–8.6 (m, 14, ArH); *m/e* (rel intensity) 310 (100), 233 (4), 165 (6), 105 (9), 77 (10).

Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.38; H, 4.58; N, 7.95. Found: C, 78.70; H, 4.80; N, 8.16.

Further elution with benzene (1 l.) afforded a viscous oil which on crystallization from alcohol furnished an additional amount of the *O*-acetate (**2**, 0.25 g), the total yield being 22%.

Repetition of the same experiment using the *O*-acetate **2** (2 g), acetic anhydride (10 ml), and anhydrous sodium acetate (1 g) as the reactants yielded the same oxazoloquinazolinone **3** (1 g), and part of the starting material (0.5 g) was recovered unchanged.

Formaldehyde from 3 by Ozonolysis. Ozonized oxygen was bubbled through a solution of **3** (0.15 g) in chloroform (10 ml) at −5 to 0° for 2.5 hr. The reaction mixture was then poured into a slurry of zinc dust and water and rapidly steam distilled. The aqueous part of the distillate was treated with a solution of dimedone (0.2 g) in alcohol (10 ml), concentrated, and extracted with chloroform, and the solvent was evaporated. The major unreacted dimedone was recovered by crystallization of the residue from benzene and the mother liquor on chromatography yielded methylenebisdimedone (18 mg), mp 188–189°, identical (mmp) with an authentic specimen prepared from formaldehyde and dimedone.

The residue remaining after steam distillation yielded unconverted **3** (75 mg) on extraction with chloroform and chromatography.

Hydrolysis of 3. A. Formation of 2-(1′-Ethoxydiphenylmethyl)-4-quinazolinone (5) and 1. Compound **3** (0.1 g) was refluxed with 5% ethanolic HCl (6 ml) for 4 hr. After cooling, the solid product was filtered, washed with water, dried, and chromatographed. Elution with 25% chloroform in benzene (250 ml) yielded 60 mg of **5**, crystallizing from benzene–petroleum ether in prisms: mp 200–202°; ir 3144, 3039, 1672 and 1607 cm^{-1}; nmr δ 1.32 (t, 3, $-CH_2-CH_3$, J = 7 Hz), 3.28 (q, 2, $-CH_2-CH_3$, J = 7 Hz), 7.3–8.0 (m, 13, ArH), 8.45 (dt, 1, C_5H), 10.33 (br, 1, –CONH); *m/e* (rel intensity) 356 (M^+, 3), 328 (8), 327 (30), 314 (3), 313 (22), 312 (100), 311 (15), 310 (10), 211 (8), 183 (10), 165 (13), 152 (3), 105 (72), 78 (60), 77 (59).

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.87. Found: C, 77.90; H, 5.74; N, 7.63.

Further elution with chloroform (150 ml) afforded **1** (30 mg).

B. Formation of 1-Acetyl-2-(1′-ethoxydiphenylmethyl)-4-quinazolinone (6). Compound **3** (50 mg) was refluxed with 1% ethanolic acetic acid (5 ml) for 4 hr. It was concentrated and cooled when **6** (51 mg) was separated as colorless plates: mp 158–159°; ir 1705, 1695, 1630, and 1605 cm^{-1}; nmr δ 1.18 (t, 3, $-O-CH_2-CH_3$, J = 7 Hz), 2.11 (s, 3, $-COCH_3$), 3.38 (a centrosymmetric multiplet, 2, $-O-CH_2-CH_3$), 7.2–8.0 (m, 13, ArH), 8.37 (dd, 1, C_5H, J = 7.5, 1.5 Hz).

Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.04. Found: C, 75.40; H, 5.61; N, 6.98.

C. Formation of *N*-Acetylanthranilic Acid. Compound **3** (0.2 g) was refluxed with 5% ethanolic KOH (12 ml) for 1 hr. After cooling and dilution with water, it was extracted with chloroform. The oily product (0.11 g) was chromatographed to yield benzophenone (45 mg) and **1** (65 mg).

The aqueous part was acidified with HCl and extracted with chloroform, and the solvent was evaporated. The residue (68 mg) on crystallization from benzene–methanol furnished *N*-acetylanthranilic acid as fine colorless flakes (35 mg), mp 183–184°, identified by direct comparison with a synthetic specimen.

***N*-Acetylanthranilic Acid from 6.** Compound **6** (0.1 g) was hydrolyzed with 5% ethanolic KOH (6 ml) for 0.5 hr yielding benzophenone (32 mg), **1** (10 mg), and *N*-acetylanthranilic acid (35 mg).

Attempted Hydrogenation of 3. A solution of compound **3** (0.2 g) in ethanol (50 ml) was stirred in an atmosphere of hydrogen in the presence of 10% Pd/C (75 mg) for 3 hr. It was filtered, and the filtrate was concentrated and allowed to crystallize to obtain the unconverted starting material (0.19 g).

Transformation of 3 and 6 to *O*-Acetate 2. When solutions of **3** or **6** in ethyl acetate with a few drops of $HClO_4$ or in THF with concentrated HCl were stirred separately at room temperature for 1 hr, the *O*-acetate **2** was obtained in quantitative yield in each case.

However, compound **3** was recovered unchanged when stirred with 1% ethanolic acetic acid at room temperature for 2 hr.

Conversion of 2 to 1 and 5. Compound **2** (0.1 g) was refluxed with 5% ethanolic HCl for 4 hr. The crude product obtained after usual work-up on chromatographic resolution furnished **1** (55 mg) and **5** (30 mg).

Treatment of 2-(α-Hydroxybenzyl)- and 2-(1′-Hydroxyisopropyl)-4-quinazolinones (7 and 8) with Acetic Anhydride and Sodium Acetate. Compound **7** (0.1 g) was refluxed with acetic anhydride (2 ml) in the presence of anhydrous sodium acetate (0.05 g) for 2 hr. After usual work-up, the crude product was crystallized from benzene–petroleum ether to get the *O*-acetate (**9**, 94 mg): mp 164–165°; ir 1750, 1220 cm^{-1}.

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.80; N, 9.52. Found: C, 69.58; H, 5.06; N, 9.31.

Compound **8** under identical conditions afforded, in quantitative yield, the *O*-acetate **10**: mp 183–184° (benzene–petroleum ether); ir 1745, 1250 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.39; H, 5.74; N, 11.37. Found: C, 63.53; H, 5.67; N, 11.24.

2-Methyl-3-(*o*-hydroxymethylphenyl)-4-imino-5,5-diphenyloxazolidine (13) from 6 and 3. A solution of 1-acetyl-2-(1′-ethoxydiphenylmethyl)-4-quinazolinone (**6**, 1.3 g) in dry ethanol (20 ml) was refluxed for 5 hr with $NaBH_4$ (1.3 g) with constant stirring. The refluxing was continued for 4 hr more after further addition of borohydride (1.3 g). Most of the alcohol was distilled off under reduced pressure. The crude product (1.05 g) obtained after usual work-up was crystallized from methanol to get the unconverted starting material (0.3 g), mp 158–159°. The mother liquor on purification through chromatography and crystallization afforded **13** (0.60 g, 50%): mp 150–151°; ir ($CHCl_3$) 3525, 3300, 1650, 1582, 995 cm^{-1}; nmr (100 MHz) δ 1.52 (d, 3, $CH-CH_3$, J = 6 Hz), 2.33 (br, 1, –OH), 4.3 and 4.38 (pair of AB doublets, 1 H each, $-CH_2-$, J_{AB} = 13 Hz), 5.67 (q, 1, $CH-CH_3$, J = 6 Hz), 6.8–8.3 (m, 15, ArH and =NH); *m/e* (rel intensity) 358 (M^+, 100), 343 (5), 340 (1), 325 (4), 314 (4), 297 (11), 295 (5), 283 (4), 210 (48), 209 (52), 193 (5), 182 (2), 176 (12), 167 (23), 166 (84), 165 (55), 158 (9), 152 (2), 147 (3), 134 (7), 133 (7), 132 (7), 131 (6), 122 (7), 105 (27), 77 (11).

Anal. Calcd for $C_{23}H_{22}N_2O_2$: mol wt, 358.167480. Found by high resolution mass spectrometry: mol wt, 358.167969.

Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.83. Found: C, 77.40; H, 6.35; N, 7.98.

Compound **3** (0.1 g) was also refluxed with $NaBH_4$ (0.2 g) in dry ethanol (10 ml) for 6 hr. The crude oily product (85 mg) on chromatographic resolution gave **13** (50 mg), mp 150–151°, and the unconverted starting material (30 mg), mp 164–165°.

Acetylation of 13 to *O,N*-diacetate (15). Acetic anhydride (0.5 ml) was added to a solution of **13** (0.1 g) in pyridine (0.2 ml) and kept overnight at room temperature. Usual work-up gave an oil which on chromatography afforded the diacetate **15** (95 mg) as a glass: ir 1735, 1680, 1650 sh cm^{-1}; *m/e* (rel intensity) 442 (M^+, 28), 400 (12), 385 (2), 369 (2), 357 (10), 340 (2), 325 (3), 313 (7), 297 (13), 295 (9), 280 (3), 260 (3), 210 (92), 209 (96), 182 (3), 175 (11), 166 (100), 165 (99), 158 (12), 132 (35), 105 (33), 77 (21).

Catalytic Hydrogenation of 13 to 14. Oxazolidine **13** (0.3 g) in ethylacetate (12 ml) containing five drops of perchloric acid was hydrogenated in the presence of 10% Pd/C (75 mg) for 1.5 hr. After filtration, the filtrate was washed successively with dilute ammonia and water, and the solvent was evaporated. The crude product (0.28 g) was crystallized from petroleum ether to get **14** (0.24 g, 84%) as colorless plates: mp 122–123°; ir ($CHCl_3$) 3420, 1650, 1582, 1345 cm^{-1}; nmr δ 1.61 (d, 3, $CH-CH_3$, J = 5.5 Hz), 1.89 (s, 3, $-CH_3$), 5.7 (q, 1, $CH-CH_3$, J = 5.5 Hz), 5.87 (br, 1, =NH), 6.7–8.3 (m, 14, ArH); *m/e* (rel intensity) 342 (M^+, 33), 327 (14), 299 (8), 298 (7), 297 (7), 283 (6), 210 (59), 209 (70), 193 (9), 182 (7), 175 (5), 166 (100), 165 (96), 160 (10), 152 (7), 132 (14), 118 (66), 105 (65), 91 (35), 77 (62).

Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48. Found: C, 80.80; H, 6.81.

Acetylation of 14 to *N*-Monoacetate (16). Compound **14** (50 mg) was heated on a steam-bath with acetic anhydride (1 ml) and

pyridine (0.5 ml) for 2 hr. After work-up, the crude product was crystallized from benzene–petroleum ether to give the acetate **16** (35 mg) in needles: mp 148–149°; ir 1680, 1650 sh cm^{-1}; nmr (100 MHz) δ 1.68 (d, 3, CH-CH_3, J = 5.5 Hz), 1.74 (s, 3, -CH_3), 2.34 (s, 3, N-CO-CH_3), 5.4 (q, 1, C**H**-CH_3, J = 5.5 Hz), 6.5–7.5 (m, 14, ArH); *m/e* (rel intensity) 384 (M^+, 51), 342 (2), 327 (2), 297 (9), 280 (3), 210 (92), 209 (94), 202 (3), 194 (8), 182 (2), 175 (3), 166 (100), 165 (95), 159 (30), 152 (3), 132 (4), 118 (8), 116 (31), 105 (34), 91 (25), 77 (24).

Anal. Calcd for $C_{25}H_{24}N_2O_2$: mol wt, 384.18376. Found by high resolution mass spectrometry: mol wt, 384.18229.

Attempted Hydrolysis of 13 and 14. Compounds **13** and **14** were recovered unchanged after refluxing with 5% ethanolic HCl or KOH for 2 hr.

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Registry No.—**1**, 18963-82-1; **2**, 18963-83-2; **3**, 52827-39-1; **5**, 52827-40-4; **6**, 52827-41-5; **7**, 13182-44-0; **8**, 52827-42-6; **9**, 13182-40-6; **10**, 52827-43-7; **13**, 52827-44-8; **14**, 52827-45-9; **15**, 52827-46-0; **16**, 52827-47-1; *N*-acetylanthranilic acid, 89-52-1.

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(15) All melting points were determined in open capillaries and are uncorrected. Unless otherwise stated, the nmr spectra were recorded in a 60-MHz Varian instrument in $CDCl_3$ with TMS as internal standard, and ir spectra were taken in Nujol mull in a Perkin-Elmer Infracord spectrophotometer (Model 137). Silica gel was used throughout for column chromatography and anhydrous Na_2SO_4 as the drying agent. Microanalyses were done by Dr. R. D. Macdonald, Micro-Analytical Laboratory, University of Melbourne, Australia.

Electrochemical Reductive Acylation of Benzophenone[1]

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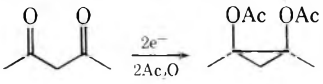
Polarographic and cyclic voltammetric studies of benzophenone in acetonitrile were carried out in the presence and absence of acetic anhydride, using tetraethylammonium bromide or perchlorate as supporting electrolytes. From the variation of pertinent parameters in these studies and from the known electrochemical behavior of benzophenone, a mechanism is proposed for the reduction of benzophenone in the presence of acetic anhydride. The results of controlled potential electrolysis substantiate the proposed mechanism.

There are many examples in the literature of electroorganic synthesis, defined as the transformation of one organic molecule into another by the action of an electric current.[2] In a number of cases involving cathodic processes, a radical anion produced by initial electron transfer undergoes followup chemical reactions in which one or more protons are abstracted from the reaction medium. We have for some time been interested in generating reactive species electrochemically and in studying their reactions with reagents other than proton donors. Our initial foray into this area[3] involved the reduction of 1,3-diketones in aprotic solvents in the presence of acetic anhydride, which led ultimately to the formation of 1,2-cyclopropanediol diacetates (eq 1), the products of intramolecular pinacol reduction. It



(1)

was of some interest to examine the behavior of monoketones under similar conditions, and this paper reports the results of our investigation of benzophenone.

Electrochemical reduction of aromatic carbonyl compounds in aqueous and aprotic media has been extensively studied.[4–16] In particular there have been studies of the electrochemical reduction of benzophenone in dimethylformamide[12–14,16] and in pyridine.[15] These studies have shown that in aprotic solvents benzophenone undergoes an initial one electron reduction to form an anion radical intermediate **1**. Further reduction results in the formation of dianion **2**. Utilizing the techniques of polarography, cyclic voltammetry (CV), and large-scale controlled potential electrolysis, we have now studied the electrochemical behavior of benzophenone in acetonitrile containing acetic anhydride with tetraethylammonium bromide (TB) or perchlorate (TP) as the supporting electrolyte. As a result of these studies, we propose the following reaction scheme for the reduction of benzophenone under these conditions.

$$Ph_2C{=}O + e^- \longrightarrow [Ph_2C{-}O]\cdot^- \quad (\mathbf{1})$$

$$\mathbf{1} + e^- \longrightarrow Ph_2\bar{C}{-}O \quad (\mathbf{2})$$

$$Ph_2C{=}O + e^- \longrightarrow \mathbf{1} \xrightarrow{Ac_2O} Ph_2\dot{C}{-}OAc \quad (\mathbf{3})$$

$$\mathbf{3} + e^- \longrightarrow Ph_2\bar{C}{-}OAc \xrightarrow{Ac_2O} Ph_2C(COCH_3){-}OAc \quad (\mathbf{4}\rightarrow\mathbf{5})$$

Table I
Polarographic Behavior of Benzophenone in the Presence of Acetic Anhydride in 0.1 *M* TP–Acetonitrile

Benzophenone concn, m*M*	Acetic anhydride concn, m*M*	Wave I			Wave II			$i_I + i_{II}$
		$-E^1/_2$, V	i_d, μA	Slope, mV	$-E^1/_2$, V	i_d, μA	Slope, mV	
2.0	0	1.83	7.78	61	2.09	6.48	120	14.26
2.0	2.0	1.81	12.3	65	2.09	1.48		13.8
2.0	4.0	1.79	13.8	72				13.8
2.0	10.0	1.77	15.3	80				15.3

Table II
Cyclic Voltammetry of Benzophenone in 0.1 *M* TB–Acetonitrile Containing Acetic Anhydride

Benzophenone concn, m*M*	Acetic anhydride concn, m*M*	Wave I					Wave II	
		$-E_{p_c}$, V	$-E_{p_a}$, V	ΔE_p, mV	i_{p_c}, μA	i_{p_a}, μA	$-E_{p_c}$, V	i_{p_c}, μA
2.0	0	1.86	1.79	70	13.62	10.65	2.26	6.24
2.0	1.0	1.85	1.79	60	13.66	8.55	2.25	3.43
2.0	2.0	1.84	1.79	50	14.58	5.09	2.19	1.62
2.0	4.0	1.76			21.75			
2.0	10.0	1.75			23.17			

Results and Discussion

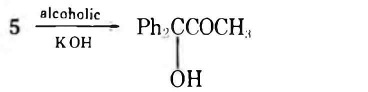
Polarography.[17] In acetonitrile with 0.1 *M* TP as supporting electrolyte, benzophenone shows two one-electron reduction waves, I and II, at $E_{1/2} = -1.83$ and -2.09 V. Acetic anhydride undergoes no reduction in this potential range. In the presence of acetic anhydride wave I grows in height (Table I) and wave II decreases until at a 2:1 ratio of anhydride to ketone the current due to wave II is immeasurably small. Further increase in the anhydride concentration then leads to relatively smaller increases in the height of wave I. Concurrently with its effect on the limiting currents, addition of acetic anhydride produces an anodic shift in the $E_{1/2}$ of wave I. These observations are consistent with the proposed mechanism. Wave I corresponds to the reduction of benzophenone to the radical anion **1**. In the absence of acetic anhydride **1** is then further reduced at a more cathodic potential to dianion **2**, giving rise to wave II. Addition of acetic anhydride diverts a fraction of the radical anion to **3**, decreasing the height of the second wave. The radical **3** is more reducible than benzophenone and immediately picks up a second electron to form acylated anion **4**. Addition of the second electron in the presence of acetic anhydride causes the first wave to increase in height and to shift to more cathodic potentials. At a sufficiently large anhydride concentration the net process occurring at the first wave will correspond to an overall transfer of two electrons, causing the limiting current to double. As indicated in Table I, the current does very nearly double for a 5:1 ratio of anhydride to ketone. The mechanism further requires that the total current for waves I and II remain constant, as is indeed observed (Table I, last column). The slopes observed for the two waves (Table I) suggest that wave I is nearly reversible in the absence of acetic anhydride (the theoretical slope for a reversible one electron process at 25° is 56 mV), but that wave II is irreversible. Further evidence bearing on the reversibility of the electron transfer steps was obtained by cyclic voltammetry.

Cyclic Voltammetry at the Hanging Mercury Drop Electrode.[18] Cyclic voltammetry data on benzophenone are given in Table II. In the absence of acetic anhydride, benzophenone shows two cathodic waves and one anodic wave. The two cathodic waves occur at potentials close to those observed polarographically and can be ascribed to successive reduction to **1** and **2**. By scanning the potential to a point midway between waves I and II, the single anodic wave at -1.76 V was established as arising from reoxidation of radical anion **1**. The resulting couple is not perfectly reversible, as both ΔE_p and i_{p_c}/i_{p_a} deviate from the theoretical values of 56 mV (for a one electron transfer) and unity, respectively. At the scan rate employed, the second wave, corresponding to formation of dianion **2**, is chemically and electrochemically irreversible. It is probable that **2** rapidly abstracts one or more protons, either from the solvent or from adventitious proton donors, to give nonreoxidizable products. Information on the reversibility of the two electron transfer steps obtained from cyclic voltammetry data agree well with the deductions made from polarographic studies.

When acetic anhydride is added to a solution in which benzophenone is undergoing reduction, trapping of radical anion **1** leads to an increase in the cathodic half of wave I as species **3** is generated and further reduced. Removal of **1** from solution means that less dianion **2** can be formed and explains the decrease with increasing anhydride concentration of i_{p_c} for wave II. The absence of any anodic waves at high anhydride concentration suggests that **4** undergoes a further rapid acylation to produce electroinactive ketoacetate **5**. Evidence for the ultimate formation of **5** is given below. It might be noted that much of the electrochemical behavior of benzophenone in acetonitrile in the presence of acetic anhydride parallels its behavior in pyridine and dimethylformamide containing proton donors.[12,15]

Large-Scale Controlled Potential Electrolysis. Further evidence supporting the proposed mechanism was provided by the large-scale electrolysis of benzophenone in the presence of acetic anhydride in acetonitrile at a potential slightly more cathodic than the first cathodic wave. At this potential the anion radical of benzophenone should be the primary product of the electrode reaction. The crude electrolysate, after removal of solvent and supporting electrolyte, was a dark brown viscous liquid. Gas chromatographic (gc) analysis revealed the presence of a single volatile product. While small amounts of this product could be separated by preparative gc, it was found more convenient to chromatograph the crude product on silica gel in order to obtain larger amounts. In this way, the electrolysis product was obtained as a colorless viscous liquid. A variety of evidence indicated that this was the postulated ketoacetate **5**. Infrared spectroscopy revealed the presence of two carbonyl groups absorbing at 1750 and 1725 cm^{-1}, positions typical of acetate esters and aliphatic ketones, respectively. Nmr also showed two slightly different C-methyl groups at 1.95 and 2.02 ppm, positions typical of methyl attached to carbonyl carbon. The aromatic hydrogens of **5** appeared as a complex multiplet centered near 7.2 ppm. As required by

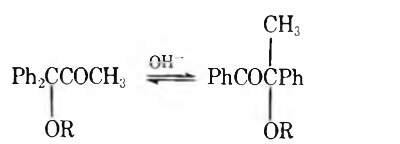
structure **5**, the integrated intensities of aryl and methyl hydrogens were very near the expected ratio of 5:3. Finally, elemental analysis of a carefully purified sample agreed well with structure **5**. The compound corresponding to **5**. 1,1-diphenyl-1-acetoxy-2-propanone, has been reported as a solid, mp 52.5–53.0,[19] and as a viscous oil.[20] The properties of our material are identical with those of the Italian workers.[20] In particular, the ir and nmr spectra of our **5** agree exactly with theirs. Prolonged efforts to cause our sample to crystallize were unavailing. The source of conflict between the two groups of workers is not known, but it may be related to the propensity of this system to undergo rearrangement.[21] Indeed, when we attempted to confirm the identity of **5** by alkaline hydrolysis to 1,1-diphenyl-1-hydroxy-2-propanone (**6**) (eq 2), the crude product showed its



(2)

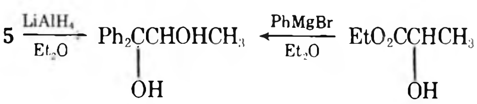
6

most prominent band in the ir at 1670 cm^{-1}, a position typical of aryl ketones. This suggests that either **5** or **6** or both underwent rearrangement in the course of the hydrolysis (eq 3). In fact, the transposition of groups represented by



(3)

eq 3 has been reported previously by Elphimoff-Felkin.[21b] In order to secure structure **5**, the electrolysis product was reduced by lithium aluminum hydride to 1,1-diphenyl-1,2-propanediol (**7**), identical with material prepared[22] by an unambiguous route (eq 4). The yield of **5** from the bulk



(4)

7

electrolysis was 66% of chromatographically pure material. The rest of the crude electrolysis product was a highly colored material which was not volatile at 230° (gc) and could not be eluted from a silica gel column with the usual solvent systems. No further attempts were made to characterize this material. It is noteworthy, however, that electrolysis of acetic anhydride alone under the same conditions yielded a substantial amount of a similar nonvolatile, highly colored material. Because of the formation of this product, reliable coulometric information could not be obtained.

Ketoacetate **5** can be regarded as a type of crossed acyloin or pinacol product. Such substances are often difficult to prepare by conventional synthetic techniques, and our electrochemical preparation could, in principle, be generalized to prepare other members of this class of compounds. Unfortunately, however, exploratory work with acetophenone and benzaldehyde has suggested that the electrochemical synthesis is probably limited to preparation of crossed acyloins derived from diaryl ketones only.

Experimental Section

Infrared spectra were measured on 10% solutions in carbon tetrachloride using a Beckmann IR-5A spectrometer. Nmr spectra were measured on carbon tetrachloride or deuteriochloroform solutions with a Varian A-60 spectrometer. Column chromatography was on Fisher silica gel (923) containing 15% added distilled water. An Aerograph A-90 P3 gas chromatograph equipped with an SF-96 column operated at 230° was used for gc analysis. Thin-layer chromatography was on microscope slides coated with silica gel G, using hexane–benzene mixtures for elution and iodine for spot visualization. A conventional saturated calomel electrode (sce) was employed as the reference electrode for all the electrochemical measurements.

Reagents and Chemicals. All chemicals were Fisher Certified reagents and except for acetonitrile were used without further purification. Acetonitrile was purified by the method of Forcier and Olver.[23] Tetraethylammonium bromide (TB) and tetraethylammonium perchlorate (TP) were used as supporting electrolytes. The bromide was commercially purchased. TP was prepared and purified as follows. TB (1 mol) and sodium perchlorate (1 mol) were separately dissolved in 1.5 l. of hot water. The solutions were mixed and allowed to cool. The TP which separated was repeatedly recrystallized from hot water until the filtrate gave no precipitate of silver bromide when tested with portions of silver nitrate solution. The resulting TP was dried over phosphorus pentoxide in a desiccator.

Polarography. A Sargent Polarograph Model XXI with Sargent IR Compensator Model A was used in a three-electrode system in a conventional H-type cell. The working electrode was a dropping mercury electrode and a platinum wire served as an auxiliary electrode. The benzophenone concentration was 2.0 m*M* and the acetic anhydride concentration was varied from 0 to 10.0 m*M*. Dry acetonitrile was used as the solvent with TP (0.1*M*) as supporting electrolyte. The solutions were deaerated with dry prepurified nitrogen for 20–30 min to remove oxygen, and an atmosphere of nitrogen was maintained over the solution throughout a particular experiment. The limiting or diffusion current i_d, the half-wave potential $E_{1/2}$, and the slope of the polarographic wave were all determined by standard procedures.[8]

Cyclic Triangular Wave Voltammetry (CV). The voltametric studies were carried out using standard techniques.[18] The triangular wave generator and the potentiostat were essentially the same as the instruments described by Chambers, *et al.*[24] The data were recorded on an X–Y recorder. A hanging mercury drop electrode (HDE) of approximately constant area was used as the stationary working electrode. The HDE was made by the method described by Enke and coworkers.[25] The constancy of the electrode area through a series of runs was checked by electrolyzing the initial solution at intervals in the series. As the CV studies were carried out to investigate qualitatively the follow-up reactions of the anion radical intermediate with acetic anhydride, the exact area of the electrode was not critical. A three-electrode system was employed with a sce and a platinum wire as the reference and the auxiliary electrodes, respectively. A conventional H-type cell with a total capacity of about 25 ml was used, the cathodic and anodic compartments being separated by a glass frit of medium porosity.

The CV measurements were made under aprotic conditions using dry acetonitrile as the solvent and 0.1*M* TB as the supporting electrolyte. The concentration of benzophenone was held at 2.0 m*M* and the anhydride concentration was varied from 0 to 10.0 m*M*. All solutions were thoroughly deaerated with dry prepurified nitrogen for 20–30 min to remove oxygen, and an atmosphere of nitrogen was maintained in the system. A scan rate of 230 mV/sec was used. That the working electrode was not contaminated by the products of electrolysis during the experiments with a particular series of solutions was shown by reproducing the voltammograms of the first solution of the series after the series had been completed.

Large-Scale Controlled Potential Electrolysis. Controlled potential electrolyses were carried out in a conventional three-electrode electrolysis cell constructed from a truncated 500-ml Pyrex erlenmeyer flask. A 200-ml Pyrex beaker was used as the anode compartment. The cathode and anode compartments as well as the cathode compartment and the sce were connected by bridges having fine porosity sintered glass frits. The bridges were filled with dry acetonitrile saturated with TB. A mercury pool was the working electrode (cathode), an sce the reference electrode, and a copper rod the auxiliary electrode (anode). The catholyte charge was 400 ml of 0.2 *M* TB in dry acetonitrile in which were dissolved 9.11 g of benzophenone and 38 ml of acetic anhydride. The entire system was purged with dry prepurified nitrogen for about 30 min before the start of the electrolysis, and the system was kept under a nitrogen atmosphere throughout the electrolysis. A high current, manually operated potentiostat was used to control the potential of the working electrode at a value slightly more cathodic than the E_{p_c} of the first benzophenone wave. The potential between working electrode and the sce was measured with a VTVM. The current was determined by measuring the potential drop across a precision resistor, either with a recorder or a potentiometer. Accurate coulo-

metric measurements were not possible because the current efficiency was less than 100%. The electrolysis was continued until the current dropped almost to zero. The disappearance of ketone was also followed by CV. On completion of the electrolysis, the catholyte was diluted with a very large excess of distilled water (800–1000 ml) and extracted several times with a total of 500 ml of ether. The combined ether extract was washed with several portions of distilled water, saturated sodium bicarbonate solution, again with portions of distilled water, and finally with two portions of saturated sodium chloride solution. The extract was dried overnight over anhydrous magnesium sulfate. After filtration, the ether was removed by evaporation under reduced pressure until the crude product reached a constant weight. At this point the crude product weighed 10.5 g.

An aliquot of the crude product (1.05 g) was column chromatographed on 60 g of silica gel using hexane–benzene mixtures for elution. The material (0.89 g, 66%) eluting with 3:1 hexane–benzene showed a single spot on thin-layer chromatography and was the pure ketoacetate **5**: viscous oil; nmr (CCl_4, internal TMS) δ 1.95 (s, 3), 2.02 (s, 3), 7.2 ppm (m, 10); ir (10% in CCl_4) 3030 (m), 1750 (s), 1725 (s), 1490 (m), 1450 (m), 1430 (sh), 1370 (m), 1350 (sh), 1235 (s), 1180 (sh), 1160 (m), 1080 (w), 1020 (m), 950 (m), 920 (w), 890 (m), 695 cm^{-1} (s). An analytical sample was prepared by rechromatography over silica gel. *Anal.* Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.85; H, 6.22.

$LiAlH_4$ Reduction of Ketoacetate 5. To a suspension of $LiAlH_4$ (1.5 mmol) in anhydrous ether (5 ml), a solution of the ketoacetate **5** (300 mg, 1.1 mmol) in anhydrous ether (5 ml) was added dropwise with continuous stirring. After stirring for 1 hr at room temperature, excess $LiAlH_4$ was destroyed by dropwise addition of ethyl acetate, followed by 100 ml of 10% ammonium chloride solution. The mixture was then extracted with ether, the ether extract washed with portions of distilled water and saturated sodium chloride solution, and the extract dried overnight over anhydrous magnesium sulfate. Removal of the ether by vacuum evaporation left an oily liquid (220 mg) which solidified on standing. The crude solid had a mp of 90–92°. It was purified by recrystallization from hexane: mp 95–96°; nmr ($CDCl_3$, internal TMS) δ 1.05 (d, 3, CH_3CH), 2.00 (d, 1, CHOH), 3.12 (s, 1, COH), 4.75 (m, CH–O), 7.3 ppm (m, 10, ArH); ir (10% in CCl_4) 3550 (m), 3000 (b), 1595 (w), 1490 (m), 1450 (m), 1387 (m), 1350 (m), 1320 (w), 1260 (m), 1170 (m), 1130 (w), 1100 (m), 962 (m), 920 (w), 892 (m), 877 (m), 700 (s), 654 (m), 635 cm^{-1} (m).

Synthesis of 1,1-Diphenyl-1,2-propanediol.[22] In a three-necked 500-ml flask fitted with a separatory funnel, reflux condenser, and mechanical stirrer was prepared in the conventional manner a Grignard reagent from 27 g of magnesium turnings and 181 g of bromobenzene in 450 ml of ether. The reagent was cooled in an ice bath while freshly distilled ethyl lactate (29 ml) was added slowly. The excess Grignard reagent was decomposed by the addition of 150 ml of ammonium chloride solution (50 g in 150 ml). The ether layer was separated and washed with portions of distilled water and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the ether was removed by vacuum evaporation. The crude white solid (mp 88–90°) was recrystallized several times from hexane to a constant melting point of 95–96°. The infrared and nmr spectra of this product were identical with that of the diol obtained by $LiAlH_4$ reduction of ketoacetate **5**. A mixture melting point of the two products was not depressed.

Registry No.—**5**, 13294-67-2; **7**, 52183-00-3; benzaphenone, 119-61-9.

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Selective Acylation of 2,4-Lutidine at Its 2- and 4-Methyl Groups

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2,4-Lutidine (1) has been acylated preferentially at its 2- or 4-methyl group depending on the condensing agent. It is suggested that if the metallic portion of the condensing agent can coordinate with the nitrogen atom of **1**, then the 2-methyl group of 1 is acylated; otherwise, the 4-methyl group is acylated. The acylation of 1 at its 2-methyl group has also been effected in high yields with three perfluorinated esters using phenyllithium as the condensing agent.

2,4-Lutidine (1) reacts selectively[1] with alkyl halides, aldehydes, and ketones at its 2- or 4-methyl group depending on the condensing agent.

We now report the selective lateral acylation of the 2- and 4-methyl groups of **1**. Earlier it was shown that 2-picoline[2] and 4-picoline[3] can be laterally metalated, the former by organolithium reagents and the latter by sodium amide in liquid ammonia.

Only one acylation of 1 could be found in the literature; its benzoylation using phenyllithium as the condensing agent[4,5] gave exclusively 4-methyl-2-phenacylpyridine in good yield. These results agree with a later study by Teague, *et al.*,[6] who showed that the reaction of 1 with benzaldehyde using phenyllithium gave exclusively 1-phenyl-2-(4-methyl-2-pyridyl)ethanol.

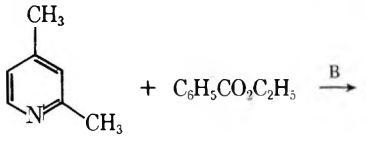
In the present study, 1 was acylated with ethyl benzoate

Table I
Monobenzoylation of 2,4-Lutidine with Ethyl Benzoate[a]

Condensing agent	% 2,4-lutidine recovered	% yield of 4-methyl-2-phenacyl-pyridine	% yield of 2-methyl-4-phenacyl-pyridine	% yield of azomethine addition product
n-Butyllithium	44	67[b,c]	3[b,d]	11[e]
Phenyllithium	50	72[b,c]	0	5[f]
Sodium amide	49	0	85[b,d]	0
Phenylsodium	53	60[b,c]	12[b,d]	*g*

[a] Molar ratio of tar base–condensing agent–ester is 2:2:1 in all the reactions. [b] Yield based on ester. [c] Mp 57.0–58 2° (from ethanol–water). *Anal.* Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6 20; N, 6.63. Found: C, 79.51; H, 6.12; N, 6 55. For the literature value [bp 159–160° (1.8 mm)], see ref 4. Picrate, mp 155.5–156.5° [lit. value 167–168° (see ref 4) and 153° (see ref 5)]. *Anal.* Calcd for $C_{20}H_{16}N_4O_8$: C, 54.54; H, 3.66; N, 12.72. Found: C, 54.69; H, 3.80; N, 12.77. [d] Bp 136–144° (0.25 mm), mp 80.8–81.8° (from aqueous ethanol). *Anal.* Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.41; H, 6.16; N, 6.58. Picrate, mp 144.0–145.5°. *Anal.* Calcd for $C_{20}H_{16}N_4O_8$: N, 12.72. Found: N, 12.60. [e] Infrared spectrum showed a relatively strong aliphatic C–H stretching band at 3.40 μ and an absorption band at 11.85 μ, characteristic of a 2,4,6-trialkylpyridine (see ref 17); the nmr spectrum is in good agreement with 2-*n*-butyl-4,6-dimethylpyridine. [f] Infrared (absorption peaks at 11.8 and 12.9 μ) and nmr spectra are in good agreement with 2,4-dimethyl-6-phenylpyridine. [g] Not determined.

in good to high yields using four different condensing agents (Table I). In all the reactions a 2:2:1 molar ratio of the tar base–condensing agent–ester was used.[7] Theoretically, two isomeric ketones, **2** and **3**, can be formed.



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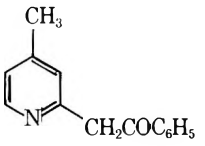

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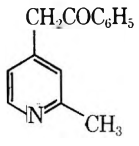


3

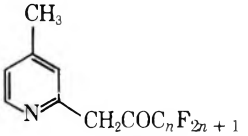
The benzoylation of **1** using *n*-butyllithium and phenyllithium gave **2** almost exclusively whose structure was assigned from its nmr spectrum. In addition small amounts of the azomethine addition products, 2-*n*-butyl-4,6-dimethylpyridine (11%) and 2-phenyl-4,6-dimethylpyridine (5%), were formed. By contrast, sodium amide in liquid ammonia gave only **3** (85%), whose structure was supported by its nmr spectrum. In addition, employing phenylsodium in benzene there was obtained **2** (60%) and **3** (12%). We agree with the suggestion made by Kaiser, *et al.*,[1] that *n*-butyllithium and phenyllithium metalate **1** essentially only at the 2-methyl group *via* the coordination of the lithium cation on the ring nitrogen atom.

In the benzoylation of **1** using phenylsodium in benzene as the condensing agent, the preference for metalation at the 2-methyl group is considerably less than with phenyllithium in ether. This result can be rationalized. The carbon–sodium[8] bond in phenylsodium (A) is more ionic than the carbon–lithium[8] bond in phenyllithium (B). Thus, A acts as a stronger base than B and removes a proton from both the 2- and 4-methyl groups of **1** to give the corresponding monosodium derivatives. The fact that a proton on the 2-methyl group is removed more extensively than a proton on the 4-methyl group suggests that A, although it probably does so to a smaller degree than B, complexes with the ring, nitrogen atom. This would enable the anionic portion of the phenylsodium to remove a proton more effectively from the 2- than from the 4-methyl group of **1**.

In contrast with these results the use of sodium amide in anhydrous liquid ammonia gave essentially exclusive metalation of the 4-methyl group of **1**. Kaiser, *et al.*,[1] have observed that **1** is alkylated at the 4-methyl group using similar reaction conditions. These workers[1] suggest two explanations for their results: (1) the sodium cation is not as effective as the lithium cation in coordinating with the nitrogen atom of **1** and (2) the sodium cation of sodium amide is complexed with ammonia molecules with the result that the amide ion is more available for ionizing the more acid hydrogen atoms of the 4-methyl group. We propose an alternate explanation, *viz.*, a steric effect may be involved *via* hydrogen bond formation between the nitrogen atom of **1** and the liquid ammonia solvent.[9] The presence of a bulky group attached to the nitrogen atom of **1**, as represented by ammoniated **1**, could offer steric hindrance to the approach of the sodium amide to the 2-methyl group and thus reduce the tendency for metalation at this group.

2,4-Lutidine (**1**) was also acylated with ethyl propionate using sodium amide in liquid ammonia as the condensing agent to give 2-methyl-4-(propionylmethyl)pyridine (45%) and the carbinol, 2-ethyl-1,3-bis(2-methyl-4-pyridyl)propanol-2.

In addition (Table II), **1** was acylated with three perfluoroalkyl esters using phenyllithium. Results comparable to the benzoylation of **1** were obtained to give ketones of type **4**. Higher yields of ketones were obtained using the reverse



4, n = 1–3

addition technique, *i.e.*, 2-lithiomethyl-4-methylpyridine was added to the esters, than when the esters were added to the tar base anion.

Although **1** can be metalated at the 4 position by sodium amide when the reaction is effected in liquid ammonia, *vide supra*, this system cannot be used to effect its acyla-

Table II
Ketones of the Type 4-$CH_3C_5H_3CH_2COR$-2

Ester	R	Yield, %	Mp, °C	Formula	Anal., % Calcd C	Calcd H	Found C	Found H
$CF_3CO_2C_2H_5$	CF_3	72.6,[a] 91.2[b]	130.5–131.2[c]	$C_9H_8F_3NO$[d]	53.20	3.94	53.07	4.17
$C_2F_5CO_2C_2H_5$	C_2F_5	42.5,[a] 83.8[b]	135.6–138[c]	$C_{10}H_8F_5NO$[e]	47.43	3.16	47.43	3.14
n-$C_3F_7CO_2C_2H_5$	n-C_3F_7	45.0,[a] 60.0[b]	110.5–111.6[c]	$C_{11}H_8F_7NO$[f]	43.56	2.64	43.32	2.77

[a] SA, standard addition. [b] RA, reverse addition. [c] From Skelly B. [d] Olive green copper salt, mp 230–232°. [e] Brown copper salt, mp 211.5–214.0°. [f] Tan copper salt, mp 185.0–186.0°.

tion with perfluoroalkyl esters since they are rapidly ammonolyzed.[10,11]

To avoid the use of liquid ammonia in preparing 2-methyl-4-picolyl perfluoroalkyl ketones attempts were made to prepare the 2-methyl-4-picolyl anion in the absence of liquid ammonia. The ammonia in a mixture of sodium amide and liquid ammonia was replaced by THF and 1 was then added. After a 6.5-hr reflux period ethyl trifluoroacetate was added to a solution to give a small amount (<1 g) of the 2-acylated product, 4-methyl-2-trifluoroacetyl methylpyridine. Extending the anion formation time to 44 hr resulted in the formation of this product in only an 11% yield.

These results indicate that anion formation involving 1 occurs at the 2-methyl group with sodium amide in THF, whereas metalation by sodium amide in liquid ammonia occurs at the 4-methyl group. Sodium amide in the somewhat polar solvent THF probably metalates the 2-methyl group of 1 for a reason comparable, *vide supra*, to the metalation of this methyl group by phenyllithium in ether and *n*-butyllithium in hexane.

It was desirable to attempt the acylation of 1 in a solvent which can solvate cations. By preferentially complexing with the potentially available sodium ion of sodium amide such a solvent would inhibit complexing between the sodium cation with the pyridyl nitrogen atom and would allow the amide ion to remove a proton from the more reactive 4-methyl group.[12,13]

Because dimethyl sulfoxide (DMSO) has been reported[14] to strongly solvate cations, it was the logical choice. To test the feasibility of this reaction, the acylation of 1 with ethyl benzoate was attempted using the DMSO anion, the strongest base which can exist in a DMSO solution,[15] as the condensing agent. The desired 4-acylated compound, 2-methyl-4-phenacylpyridine, was obtained in low yield (19%). Unfortunately, the reaction could not be extended to include the acylation of the 4-methyl group of 1 by perfluorinated esters since several attempts gave only polymeric materials.

Infrared and nmr spectroscopy were used to confirm the structure of 4-methyl-2-phenacylpyridine. Our results agree with those of Branch, *et al.*,[16] who have shown that this and related ketones do not exist in the keto form but rather in a conjugated chelated form. By contrast, the infrared spectrum of the solid ketone, 2-methyl-4-phenacylpyridine, showed a strong C=O absorption band at 5.95μ microns and no evidence of conjugate chelation.

Experimental Section

(1) General Procedure for Acylation Reactions. Acylation of 2,4-Lutidine Using Lithium Bases. All monoacylations of 2,4-lutidine were carried out using the procedure of Levine, *et al.*,[2] for the acylation of 2-picoline with esters using phenyllithium as the condensing agent.

(2) Acylation of 2,4-Lutidine and Its Derivatives. Acylation of 2,4-Lutidine with Esters Using Various Condensing Agents. (a) Using a 2:2:1 Molar Ratio of 2,4-Lutidine:*n*-Butyllithium:Ethyl Benzoate. To *n*-butyllithium (0.4 mol as a 1.61 *M* solution in *n*-hexane) in 400 ml of anhydrous ether was added 2,4-lutidine (0.4 mol, 42.8 g) over a 20-min period. The solution was stirred for 30 min at room temperature. Ethyl benzoate (0.2 mol, 30.0 g), dissolved in an equal volume of anhydrous ether, was added (25 min). The solution was stirred for 45 min at room temperature and processed in the customary manner. Distillation of the crude product mixture gave (a) 23.7 g of light yellow liquid, bp 75–128° (50 mm), and (b) 31.3 g of 4-methyl-2-phenacylpyridine, bp 154–160° (1.3 mm). Fraction a was analyzed by gas chromatography and was shown to consist of two compounds: (1) 2,4-lutidine (79%) and (2) 2-*n*-butyl-4,6-dimethylpyridine (21%). The ir spectra of the ketone in both liquid and solid forms are in good agreement with the assigned structure, 4-methyl-2-phenacylpyridine.[16] Although the nmr spectrum of the ketone taken prior to recrystallization agrees essentially with the proposed structure, 4-methyl-2-phenacylpyridine, three minor extraneous peaks are present at 6.02, 7.62, and 9.05 ppm. The peak at 9.05 ppm indicates the possible presence of an *n*-alkyl group possibly attributable to the *n*-butyl group in 2-*n*-butyl-4,6-dimethylpyridine. The two peaks at 6.02 and 7.62 ppm suggest the presence of the methylene group and the 2-methyl group, respectively, of 2-methyl-4-phenacylpyridine. It was calculated that the maximum concentrations of 2-*n*-butyl-4,6-dimethylpyridine and 2-methyl-4-phenacylpyridine present in the ketone, fraction b, are 6.4 and 3.6%, respectively. These results show that the minimum ratio of acylation at the 2 position to acylation at the 4 position of 2,4-lutidine is 25:1. Thus, there were obtained 18.7 g (44% recovery) of 2,4-lutidine, 7.0 g (10.7%) of 2-*n*-butyl-4,6-dimethylpyridine, 1.1 g (2.6%) of 2-methyl-4-phenacylpyridine, and 28.2 g (67%) of 4-methyl-2-phenacylpyridine.

(b) Using a 2:2:1 Molar Ratio of 2,4-Lutidine:Phenyllithium:Ethyl Benzoate. The interaction of phenyllithium (0.4 mol, prepared from 0.8 g-atom (5.55 g) of lithium metal and 0.4 mol (62.8 g) of bromobenzene), 2,4-lutidine (0.4 mol, 42.8 g), and ethyl benzoate (0.2 mol, 30.0 g) gave (a) 21.3 g (50% recovery) of 2,4-lutidine, bp 76–80° (50 mm), (b) 3.4 g of yellow liquid, bp 118–148° (1.0 mm), and (c) 32.7 g of crude 4-methyl-2-phenacylpyridine, bp 125–145° (0.2 mm). There were obtained 21.3 g (50% recovery) of 2,4-lutidine, 3.4 g of a mixture of 2,4-dimethyl-6-phenylpyridine and 4-methyl-2-phenacylpyridine, and 32.7 g of a mixture containing 2.3 g (3.1%) of 2,4-dimethyl-6-phenylpyridine and 30.4 g (72%) of 4-methyl-2-phenacylpyridine.

(c) Using a 2:2:1 Molar Ratio of 2,4-Lutidine:Sodium Amide:Ethyl Benzoate. To 0.4 mol of sodium amide in 500 ml of anhydrous liquid ammonia was added a solution of 2,4-lutidine (0.4 mol, 42.8 g) in 50 ml of anhydrous ether over a 20-min period. A solution of ethyl benzoate (0.2 mol, 30.0 g) in 30 ml of ether was added and the mixture was stirred for 1 hr. Ammonium chloride, 25 g, was added slowly and the ammonia was removed and replaced by ether. The reaction mixture was processed by the normal procedure. Distillation gave 21.0 g (49%) of recovered 2,4-lutidine, bp 75–77° (55 mm), 36.0 g (85%) of 2-methyl-4-phenacylpyridine, bp 136–144° (0.25 mm), and 1.7 g of a tarry distillation residue. The yellow viscous, liquid ketone solidified shortly after collection, mp 80.8–81.8° from aqueous ethanol; monopicrate, mp 144.0–145.5°. The ir of the solid ketone as a Nujol mull shows a strong carbonyl band at 5.9 μ.

(d) Using a 2:2:1 Molar Ratio of 2,4-Lutidine:Phenylsodium:Ethyl Benzoate. Phenylsodium was prepared from sodium (15.9 g, 0.69 g-atom) and bromobenzene (47.1 g, 0.3 mol) in 200 ml of anhydrous toluene as described earlier.[17] To the dark brown mixture was added a solution of ethyl benzoate (0.15 mol, 22.5 g) in 25 ml of dry benzene; stirring was continued for 30 min at 10–15°. The reaction was processed by the usual procedure. Distillation gave 17.0 g (55% recovery) of 2,4-lutidine, bp 75–77° (50 mm), 22.9 g (72%) of a mixture of 4-methyl-2-phenacylpyridine and 2-methyl-4-phenacylpyridine, bp 150–157° (1.0 mm), and 2.5 g of a tarry distillation residue. The ir of the ketone mixture agrees with that of 4-methyl-2-phenacylpyridine although a small amount of 2-methyl-4-phenacylpyridine was present by comparison with the spectrum of the latter compound. The methyl protons of the 2- and 4-methyl groups on a pyridine ring have τ values of 7.64 and 7.93 ppm in the nmr spectrum. Quantitative nmr analysis showed that the ketone mixture contains 4-methyl-2-phenacylpyridine (83%) and 2-methyl-4-phenacylpyridine (17%). This corresponds to yields of 60 and 12%, respectively.

(e) Using a 2:2:1 Molar Ratio of 2,4-Lutidine:Sodium Amide:Ethyl Propionate. To 0.4 mol of sodium amide in 500 ml of anhydrous liquid ammonia was added a solution of 2,4-lutidine (0.4 mol, 42.8 g) in 50 ml of anhydrous ether. The mixture was stirred for 2 hr, followed by the addition of ethyl propionate (0.2 mol, 20.4 g) in 20 ml of ether. It was stirred for 1.25 hr and neutralized with 25 g of solid ammonium chloride, and the ammonia was replaced by ether. The reaction mixture was processed by the usual procedure. Distillation gave (a) 20.0 g (47% recovery) of 2,4-lutidine, bp 75–77° (50 mm), (b) 14.7 g (45%) of 2-methyl-4-(propionylmethyl)pyridine, bp 143–146° (14.2 mm), and (c) 11.5 g (21%) of 2-ethyl-1,3-bis(2-methyl-4-pyridyl)propanol-2, bp 175–180° (0.3 mm).

Distillate fraction a was identified as 2,4-lutidine (ir). The ir spectrum of distillate fraction b is in agreement with the assigned structure, 2-methyl-4-(propionylmethyl)pyridine (carbonyl absorption band at 5.80 μ and the absorption band at 12.35 μ, charac-

teristic of a 2,4-disubstituted pyridine derivative). The nmr spectrum of fraction b is in good agreement with the proposed structure. The absence of a significant proton resonance peak with a τ value in the range of 7.80–7.95 ppm, arising from the 4-methyl group on the pyridine ring, is evidence for essentially complete acylation at the 4 position. Fraction b was analyzed.

Anal. Calcd for $C_{10}H_{13}NO$: N, 8.58. Found: N, 8.85.

A sample of the ketone was converted to a yellow monopicrate, mp 122.8–124.2°.

Anal. Calcd for $C_{16}H_{16}N_4O_8$: N, 14.28. Found: N, 14.21.

The ir spectrum of the carbinol, fraction c, shows a very strong absorption band at 3.0 μ, characteristic of an O–H group. The nmr spectrum of this product is in good agreement with the assigned structure. The absence of a proton resonance peak at 7.80–7.95 ppm, attributable to the 4-methyl group on the pyridine ring, offers further support for essentially exclusive attack of the sodium amide at the 4-methyl group of 2,4-lutidine. The carbinol was analyzed.

Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 1036. Found: C, 75.68; H, 8.07; N, 10.18.

(3) Acylation of 2,4-Lutidine with Perfluorinated Esters. (a) Standard Addition Technique. This is the same as the general procedure used above for the other acylation reactions.

(b) Reverse Addition Technique. The acylation of the anion of 1 with an ester employing the reverse addition technique differs from the standard addition procedure in that the 2 equiv of the tar base anion is prepared from phenyllithium and 1 in a reaction vessel which is positioned above and connected to a second reaction vessel. In the bottom flask (three necked), which is equipped with a reflux condenser and a mechanical stirrer, is placed 1 equiv of the appropriate ester and 100 ml of anhydrous ether for every 0.1 mol of ester. The flask containing the ester is cooled to −5° with a salt and ice bath and the solution of the tar base anion is added dropwise. After addition of the anion the reaction mixture is allowed to warm to room temperature, stirred for 1 hr, and processed as with reactions employing the standard addition technique.

(4) The Acylation of 2,4-Lutidine at the 2-Methyl Group with Ethyl Trifluoroacetate Using the Reverse Addition Technique. Using phenyllithium (0.2 mol), 1 (21.4 g, 0.2 mol), and ethyl trifluoroacetate (14.2 g, 0.1 mol) there was obtained 8.48 g (39.6%) of 2,4-lutidine (bp 75° (42 mm)) by distillation. Upon extraction of the distillation residue with Skelly B there was obtained 18.5 g (91.2%) of 4-methyl-2-picolyl trifluoromethyl ketone (mp 130.4–131.8°) and 4.16 g of an intractable residue.

Registry No.—**1**, 108-47-4; **2**, 3197-57-7; **2** picrate, 3197-62-4; **3**, 51975-33-8; **3** picrate, 52920-03-3; **4** (n = 1), 52920-04-4; **4** (n = 1) copper salt, 52920-05-5; **4** (n = 2), 52920-06-6; **4** (n = 2) copper salt, 52920-07-7; **4** (n = 3), 52920-08-8; **4** (n = 3) copper salt, 52920-09-9; n-butyllithium, 109-72-8; phenyllithium, 591-51-5; sodium amide, 7782-92-5; phenylsodium, 1623-99-0; ethyl benzoate, 93-89-0; 2,4-dimethyl-6-phenylpyridine, 27068-65-1; ethyl propionate, 105-37-3; 2-methyl-4-(propionylmethyl)pyridine, 52920-10-2; 2-methyl-4-(propionylmethyl)pyridine picrate, 52920-11-3; 2-ethyl-1,3-bis(2-methyl-4-pyridyl)propanol-2, 52920-12-4; ethyl trifluoroacetate, 383-63-1; ethyl pentafluoropropionate, 426-65-3; ethyl heptafluorobutyrate, 356-27-4; 2-n-butyl-4,6-dimethylpyridine, 52919-93-4.

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Studies on the Coupling Step in Solid Phase Peptide Synthesis. Further Competition Experiments and Attempts to Assess Formation of Ion Pairs[1]

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Competition experiments have been performed to study the possible influence of a number of α-amino protecting groups with urethane structure on the reactivity of amino acids in the coupling step under solid phase peptide synthesis conditions. No differences in reactivity could be detected, however, by this procedure, which we recently used for a similar study on the influence of amino acid side chains. A few additional experiments have been made with peptides instead of amino acids to gain insight into the prospects of fragment coupling. The data to be presented in the first half of this paper have been obtained by amino acid analysis of hydrolyzed peptide mixtures. Insolubilized hydrogen-bonded ion pairs are postulated to be formed on addition of an amino acid derivative in dichloromethane prior to the coupling in solid phase peptide synthesis. In the second half of this paper attempts have been made to determine the extent to which ion pairs are formed under different conditions. The influence of temperature, the concentration of soluble carboxyl component, and the nature of the solvent have been studied.

Peptide synthesis on a solid support, generally called solid phase peptide synthesis (SPPS), was introduced and pioneered by Merrifield[2,3] and is today a well-established technique which has been used for the preparation of many peptides. In this procedure synthesis takes place in a stepwise fashion starting from the carboxyl end, with the growing peptide attached by an ester bond to a polystyrene resin. Since the α-amino function must be protected, one cycle involves exposing the amino group and coupling to it the next amino acid. After a certain number of such cycles the peptide is stripped off the resin. Generally all protecting groups still remaining on the peptide are removed at the same time, leaving a crude free peptide which now has to be purified.

Table I
Competition Experiments with Different N^{α}-Protecting Groups

Expt no.[a]	N^{α}-protected amino acid used (incorporation, %)				Total incorporation (%)
1	Z(OMe)-Gly (41.7)	Z(OMe)-Phe (30.8)	Boc-Leu (23.9)	Boc-Val (4.0)	100.4
2	Bpoc-Gly (41.2)	Boc-Phe (29.0)	Bpoc-Leu (22.3)	Boc-Val (4.0)	96.5
3	Bhoc-Gly (40.6)	Bhoc-Phe (31.6)	Boc-Leu (22.2)	Boc-Val (4.1)	98.5
4	Ppoc-Gly (40.6)	Ppoc-Phe (31.8)	Boc-Leu (21.9)	Boc-Val (3.7)	98.0
5	Trt-Gly (19.3)	Boc-Phe (40.6)	Boc-Leu (27.2)	Boc-Val (7.9)	95.0
A[b]	Boc-Gly (39.7)	Boc-Phe (29.6)	Boc-Leu (24.8)	Boc-Val (4.8)	98.6
6	Z(OMe)-Gly (32.9)	Boc-Ala (27.2)	Z(OMe)-Phe (23.9)	Boc-Leu (17.9)	101.9
7	Bhoc-Gly (30.1)	Boc-Ala (26.8)	Bhoc-Phe (23.6)	Boc-Leu (14.8)	95.3
B[b]	Boc-Gly (32.3)	Boc-Ala (28.8)	Boc-Phe (24.0)	Boc-Leu (20.1)	105.2

[a] Expt 1–5 and A were performed with Ala-resin and 6, 7, and B with Val-resin. [b] See ref 4.

Competition experiments[4] were recently performed to obtain information on the reactivity of individual amino acids in the coupling step. Claims in the literature[5,6] of difficulties in the coupling of specific Boc-amino acids prompted us to try to arrange different Boc derivatives according to their reactivity in the coupling step under SPPS conditions. We considered competition experiments with a Boc-amino acid and a reference compound, but the number of amino acid analyses necessary in this approach caused us to select the present, less strict procedure with four competing components, although the significance in the figures obtained is partly lost. As expected, considerable differences in reactivity were found to exist. Those experiments have now been extended. Protecting groups themselves, *e.g.* on the α-amino function or even in side chains, could possibly influence the reactivity in different ways. Bulky groups could give rise to steric hindrance in the coupling step or to reduced penetration of the amino acid derivative into the interior of the resin. For this reason we have now conducted a series of experiments where the influence, if any, of different α-amino protecting groups has been investigated.

Peptides rather than amino acids have in a few cases been used for extension of the peptide chain in SPPS. For further references, see ref 7. Consequently, we have also been interested in seeing how a peptide would perform under competition conditions. This, on the other hand, has made necessary some further experiments which could be used for purposes of comparison.

In SPPS dichloromethane is generally used as the reaction medium, with dimethylformamide (DMF) as an alternative if the amino acid derivative dissolves poorly. Both swell the resin satisfactorily. The difference in properties between the two solvents mentioned is considerable indeed, and one consequence of this will be emphasized in this paper.

The interaction between acetic acid and different amines in carbon tetrachloride and chloroform was studied by Barrow and Yerger[8] and reviewed recently by Davis.[9] Using infrared spectroscopy, different adducts, depending on the type of amine, solvent, and stoichiometry, were inferred, all of which were characterized by association *via* hydrogen bonds as ion pairs. Extrapolating these results to dichloromethane, strong interactions can be expected between the free amino terminus of the amino acid last coupled and the carboxyl group of the N-protected derivative after addition of the latter compound in the Merrifield procedure. To our knowledge this has not been considered so far, although solvents such as chloroform and dichloromethane have been used in peptide synthesis for many years. It may also explain the adsorption effect recently described by Esko and Karlsson[10] and later studied or used by Elliott, *et al.*,[11] and Losse and coworkers.[12] The latter part of this paper therefore deals with model experiments on noncovalent bonding of the carboxyl component to the amino group of an amino acid resin of Merrifield type. These experiments together with the competition experiments constitute our efforts so far toward attaining a better understanding of the coupling step in SPPS.

Table II
Competition Experiments on Fragment Coupling[a]

Expt. no.	Amino acid incorporation (%) Gly	Leu	Phe	Total incorporation (%)
8	79.1	18.8	21.1	99.1[b]
C	56.7		45.0	101.7
9A	74.7	21.6	21.7	96.5
9B[c]	77.4	22.3	22.2	99.7
D	58.3		41.0	99.3

[a] Z(OMe)-Leu-Phe[21] was used in these experiments together with Ala-resin (expt 8) and Val-resin (expt 9). [b] This value was obtained using the average found for Leu and Phe. [c] After hydrolysis for 72 hr. When not otherwise stated hydrolysis was for 24 hr.

Results and Discussion

Competition Experiments were carried out as described in the Experimental Section. Blocking groups tested and compared included the *tert*-butyloxycarbonyl[13] (Boc), *p*-methoxybenzyloxycarbonyl[14] [Z(OMe)], 2-(*p*-biphenyl)isopropyloxycarbonyl[15] (Bpoc), benzhydryloxycarbonyl[16] (Bhoc), 2-phenylisopropyloxycarbonyl[17] (Ppoc), and trityl[18] groups. Trityl amino acids are considered sterically hindered[19] (see Table I).

The experiments were performed with a polystyrene–*co*-1% divinylbenzene resin to which Boc-alanine or Boc-valine had been esterified according to Merrifield's original procedure. Prior to the coupling experiments, Boc was removed using 50% trifluoroacetic acid (TFA) in dichloromethane. A mixture of 1 equiv each calculated on the amount of amino acid resin of four different N^{α}-protected amino acids and the corresponding amount of dicyclohexylcarbodiimide (DCCI) were added and allowed to react with the resin for 2 hr. The resin was washed free from reactants and by-products, treated with 50% TFA as above, washed again, and dried. A resin sample was treated with HF,[20] the peptide mixture was extracted from the resin, and the solution was evaporated to dryness. A portion was hydrolyzed and then quantitatively analyzed for amino acids on an amino acid analyzer. The quantity found of the amino acid originally attached to the resin was arbitrarily set to 100 and the amount found of the competing amino acids was normalized accordingly. Total incorporation was obtained as the sum of the latter values. Assuming a relative experimental error of less than 3%, complete coupling reaction

Table III
Other Competition Experiments Performed

Expt no.	Protected amino acids used (incorporation, %)				Total incorporation (%)
10	Boc-Gly (33.8)	Boc-(NO_2)-Arg (27.4)	Boc-(Z)-Lys (18.6)	$(Boc)_2$-His (18.1)	97.9
11A	Boc-Gly[a] (94.9)	Boc-Ile[a] (2.6)			97.5
11B	Boc-Gly[a,b] (99.7)	Boc-Ile[a,b] (4.4)			104.1
E	Boc-Gly (68.6)	Boc-Ile[c] (29.7)			98.3

[a] Ten equivalents of each Boc derivative was used. [b] After hydrolysis for 72 hr. When not otherwise stated hydrolysis was for 24 hr. [c] See experiment 10A in ref 4; 3 equiv of Boc-Ile was used.

would give total incorporation values in the range 94–106. The results for different N^{α}-protecting groups are given in Table I.

As seen in Table I, a remarkably good agreement was obtained between expt 1–4 and A, performed with alanine attached to the resin. In our opinion this can only be due to complete noninterference by the protecting groups in the coupling step, which is then understood also to include penetration of the derivatives into the resin. Whether the protecting group has none, one, or two benzene rings in it does not seem to matter, as long as it is of urethane structure. Similarly the results of expt 6, 7, and B agree. In expt 5 the picture was different. As expected Trt-Gly coupled more poorly than other glycine derivatives studied, and in fact Boc-Phe and Boc-Leu showed higher reactivities. Since a protecting group of urethane structure does not seem to influence the coupling, it should be possible to use amino acid derivatives with different amino-protecting groups more liberally in the same synthesis. This may sometimes aid in the preparation of the protected amino acids.

Our interest in utilizing fragment condensation on a solid support was the reason for the experiments whose results are presented in Table II. In expt 8 1 equiv each of Boc-Gly and Z(OMe)-Leu-Phe[21] was allowed to react with Ala-resin for 2 hr in the presence of 2 equiv of DCCI. Experiment 9 was identical with expt 8, except that Val-resin was used. C and D were controls, performed with Boc-Phe instead of the dipeptide. Evidently, peptides show reduced reactivity in comparison with the C-terminal amino acid protected as Boc derivative. Preparative experiments have later demonstrated, however, that the remaining reactivity is high enough to secure a high yield of product as exemplified by synthesis of bradykinin using di- and tripeptide fragments.[7]

Experiment 10 in Table III presents data on the behavior of the three basic amino acids, Arg, Lys, and His, which all seem to couple well. Ala-resin was used in this experiment. Our attempts to also include Trp in the present work invariably resulted in very low "total incorporation," indicating loss of Trp due to decomposition.

Experiment 11, performed with 10 equiv of each amino acid derivative, serves to demonstrate in full magnitude the difference in reactivity between Boc-Gly and Boc-Ile. Since the Val-resin was used, an extended hydrolysis was necessary. Considering possible errors, we think it is safe to conclude that Boc-Gly is at least 20 times more reactive than Boc-Ile under the conditions used, which approximate those of SPPS. The reason for this difference in reactivity is, of course, the steric influence of the side chain of isoleucine.

Experiments on Carboxyl–Amino Group Interaction. As pointed out above, hydrogen-bonded ion pairs are known to be formed when acetic acid and an amine are mixed in carbon tetrachloride or chloroform. The rest of this paper will be devoted to model experiments to determine the extent of ion-pair formation under conditions related to SPPS.

Temperature, concentration, and the nature of the solvent are among the factors known to influence the stability of hydrogen bonds in solution. According to Pimentel and McClellan,[22] drastic effects are observed, as revealed by ir and Raman spectra, upon changes in temperature of 10–20° or upon variation of the concentration of the hydrogen bonding substances in an inert solvent. This study will illustrate the effect of changes in these three parameters on the system Boc-amino acid/polymer, where the polymer is of Merrifield type, a polystyrene matrix with a second amino acid with a free amino group attached *via* its carboxyl by an ester bond.

All following experiments were performed according to the same general scheme, the details of which are found in the Experimental Section. Boc-Phe was carefully equilibrated with Ala-resin under conditions specified with reference to solvent, temperature, and concentration of Boc-Phe. The solution was then filtered off and the resin washed twice with the same volume of fresh solvent. Dichloromethane was added, followed by DCCI, and reaction was allowed to proceed for 1 hr. The resin was carried through a normal washing procedure. Nonreacted amino groups were finally determined using the 2-hydroxy-1-naphthaldehyde procedure[23] developed in our department.

Experiments 14 and 20 above give the results for the two solvents normally used in SPPS. A high coupling yield was expected for dichloromethane.[10] These orientative experiments further demonstrate that carbon tetrachloride and benzene are even more efficient than dichloromethane in this context. At the other end of the table we find dioxane with about the same dielectric constant. Dioxane, however, has basic properties[9] and is not inert to proton donors.[22] Carbon tetrachloride and benzene have negligible acidity and basicity as well as low dielectric constants, *i.e.*, are more truly inert. It should be emphasized that all experiments in Table IV were performed under considerably more dilute conditions than normally used in preparative work.

The standard method for attachment of the first amino acid to the resin gives rise to some quaternary ammonium sites. To exclude their influence five extra experiments were performed with an Ala-resin without such sites, the results of which are given in parentheses (experiments 16 and 18–21). We interprete our results to mean that dimethylformamide and dioxane completely exclude association between the components.

The trend in the experiments of Table V was as expected.[10] By conducting experiments at a low enough temperature, dichloromethane can be brought to give results similar to those for carbon tetrachloride and benzene at room temperature.

Under concentration conditions more typical of those used in SPPS dichloromethane behaved approximately as carbon tetrachloride and benzene did at the low concentra-

tion used in Table IV. Extrapolating the results of Table IV, V, and VI, very strong association of Boc-Phe to Ala-resin can be envisaged at both high concentration and reduced temperature in dichloromethane.

Table IV
Innfluence of the Solvent on Carboxyl–Amino Group Interaction[a]

Expt. no.	Solvent	Dielectric constant (ϵ)[b]	Coupling yield[c] (%)
12	Carbon tetrachloride[d]	2.23	>99 5
13	Benzene[d]	2.27	>99 5
14	Dichloromethane[d]	9.08[e]	54–59
15	Chloroform[f]	4.81[e]	55
16	Tetrahydrofuran[f]	7.39	33 (39)[g]
17	Ethyl ether[d]	4.34[e]	28
18	HMPA[h]	30[e,i]	25 (13)[g]
19	Ethyl acetate[d]	6.02	18 (16)[g]
20	Dimethylformamide[g]	36.7	14 (0)[g]
21	Dioxane[f]	2.21	11 (0)[g]

[a] Performed at room temperature 23–25°. The resin used originally had 0.287 mmol of Ala/g. All experiments refer to a dilution of 57.1 ml/g of resin. [b] Values when not otherwise stated were taken from ref 9 and refer to 25°. [c] Determined according to ref 23. [d] "Pro analysi" quality. [e] Refers to 20°. [f] Filtered through a column of active aluminum oxide. [g] See discussion below. [h] Hexamethylphosphoramide. Kept over a molecular sieve, Linde 4A, for several weeks prior to use. [i] According to ref 24.

Table V
Influence of Temperature on Carboxyl–Amino Group Interaction[a]

Expt no.	Temp (°C)	Coupling yield (%)
22	37	30
23	23–25	54–59
24	4	95
25	−12	>99.5

[a] All experiments refer to dichloromethane. All conditions except temperature were the same as in Table IV.

Table VI
Influence of Concentration on Carboxyl–Amino Group Interaction[a]

Expt no.	Dilution (ml of solvent/g of resin)	Coupling yield (%)
26	57.1	54–59
27	28.6	73
28	14.3	93
29	7.1	>99.5

[a] All experiments refer to dichloromethane. All conditions were the same as in Table IV except dilution.

We do not want to make any definite statements about the stoichiometry. In the work of Barrow and Yerger mentioned above evidence was found not only for 1:1 adducts between acetic acid and amine but also for 2:1 adducts. Since excess of carboxyl component, normally Boc-amino acid, is always used in the SPPS procedure, it is possible that an amino group can bind more than one molecule of Boc derivative. Preliminary experiments simply involving repeated washing of the resin to recover material indicate that 6–7 additions of fresh dichloromethane[25] may be needed to remove the excess of Boc-amino acid used. After 10 washings about 0.6 equiv of Boc-amino acid had still not been recovered. No evidence for discrete adduct species was detected in this admittedly simple experiment. According to Elliott, *et al.*,[11] only the excess is removed by washing with fresh solvent.

Tables IV–VI provide fundamental data on the extent of association under different conditions between the components in the SPPS procedure. Some of the figures bear on the adsorption coupling method,[10] which has more recently proved useful in the preparation of two bradykinin analogs.[11,12a] The scope of this modified procedure, however, still remains to be determined.

Experimental Section

Acid hydrolyses of peptides were performed with 6 *N* HCl (110°, 24 hr, when not otherwise stated) in sealed evacuated tubes, and the amino acids were determined with a Biocal BC-200 or Durram D-500. Absorbance measurements were performed on a Coleman Hitachi 124 or Beckman Acta CIII to a precision of 0.001. Solvents were of standard quality when not otherwise stated. Amino acids used were of L configuration (except Gly). Resin refers to cross-linked polystyrene (1% divinylbenzene, Bio-Beads S-X-1).

Boc-Ala-resin. This was prepared like Boc-(NO$_2$)Arg-resin[26] from a chloromethylated resin with 0.75 mmol of Cl/g and after deblocking with 50% TFA/dichloromethane for 30 min gave on analysis[10] 0.287 mmol of Ala/g.

Boc-Val-resin. The same chloromethylated resin and the same procedure resulted in a product with 0.261 mmol of Val/g.

Boc-Ala-resin without Quaternary Sites. Chloromethylated resin with 1.75 mmol of Cl/g was converted to hydroxymethyl resin[27] and esterified with Boc-Ala accordingly,[27] giving a resin with 0.638 mmol of Ala/g.

Competition Experiments. A weighed sample of Boc-Ala- or Boc-Val-resin (about 300 mg) was reacted by rocking for 30 min with 3 ml of 50% TFA/dichloromethane in a 10-ml cylindrical glass vessel with a fritted disk filter, stopper, and stopcock. After washing with dichloromethane (3 × 2 min), neutralization with 10% triethylamine in the same solvent (10 min), and washing again with dichloromethane similarly, 1 equiv each (calculated on the amount of Ala or Val, bound to the resin) of generally four *different* protected amino acids was together added in 3 ml of dichloromethane; 10 min later, a corresponding amount (generally 4 equiv) of DCCI in a minimum of dichloromethane was added and coupling allowed to proceed for 2 hr. After washing with dichloromethane (3 × 2 min), the deprotection procedure was repeated, mainly to get rid of residual amino acids not covalently bound to the resin. An aliquot of dry resin was reacted with HF[20] (0°, 1 hr) and the peptide mixture was extracted from the resin with 8 × 5 ml of 10% HOAc. After evaporation of the solvents, the residue was hydrolyzed and analyzed for amino acids. 62–77% of the C-terminal amino acid could be accounted for. In expt 8 and 9 performed similarly, Z(OMe)-Leu-Phe[21] was allowed to compete with Boc-Gly.

Experiments on Carboxyl–Amino Group Interaction. A typical experiment was done as follows. A weighed amount of Boc-Ala-resin (~70 mg) was deprotected, washed, neutralized, and washed again as just described and allowed to equilibrate for 4 hr with 4 equiv of Boc-Phe in about 4 ml of solvent. The solution was filtered off, and the resin was washed twice for 2 min with the same volume of fresh solvent. Dichloromethane was added, followed by 2 equiv of DCCI in a minimal volume of the same solvent. After reaction for 1 hr, the resin was taken through a washing procedure including dichloromethane (2 × 2 min), absolute ethanol (2 × 2 min), and again dichloromethane (2 min). This was followed by determination of unreacted amino groups.[10]

Registry No.—Z(OMe)-Gly, 4596-54-7; Z(OMe)-Phe, 23234-86-8; Boc-Leu, 13139-15-6; Boc-Val, 13734-41-3; Bpoc-Gly, 23650-19-3; Boc-Phe, 13734-34-4; Bpoc-Leu, 18634-99-6; Bhoc-Gly, 3312-84-3; Bhoc-Phe, 3312-91-2; Ppoc-Gly, 52950-77-3; Ppoc-Phe, 57499-65-1; Trt-Gly, 52950-78-4; Boc-Gly, 4530-20-5; Boc-Ala, 15761-38-3; Z(OMe)-Leu-Phe, 14565-51-6; Boc-(NO$_2$)-Arg, 2188-18-3; Boc-(Z)-Lys, 2389-45-9; (Boc)$_2$-His, 20866-46-0; Boc-Ile, 13139-16-7.

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Rate Constants for Peptide *p*-Nitrophenyl Ester Coupling Reactions in Dimethylformamide. A Model for Steric Interactions in the Peptide Bond Forming Transition State[1]

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Rate constants are reported for 41 aminolysis reactions of N-protected amino acid *p*-nitrophenyl esters with amino acid ethyl or *tert*-butyl esters in DMF at 30°. With the exception of reactions involving proline esters as nucleophiles, all reactions yield rate constants which can be satisfactorily approximated as a product of two partial rate factors. A model which accounts for this observation is proposed and discussed, and generalizations to the behavior of other phenyl esters are considered.

The work described in this paper was initiated because rate constants for a number of aminolysis reactions of peptide esters of 3-acyloxy-2-hydroxy-*N*-ethylbenzamides were observed to fit the very simple rate law of eq 1, for

$$k_{A\text{-}B} = (k_{A\text{-}Gly})(k_{Gly\text{-}B})\left(\frac{1}{k_{GlyGly}}\right) \quad (1)$$

which $k_{A\text{-}B}$ is the second-order rate constant for the coupling of an active ester derived from a protected amino acid Z-A-OH with an amino acid ester, H-B-OEt.[2] This observation implies that activation energy changes for these reactions, which for the cases studied were largely sterically determined, must arise from independent effects of the substituents at the two amino acid sites, and suggests, moreover, that 400 rate constants for the possible dipeptide forming aminolyses can be estimated from only 39 measured rate constants. The *p*-nitrophenyl esters are the most widely used and easily studied of the peptide active esters, and for these reasons, we chose these esters for an investigation of the validity of eq 1. Although an aqueous medium as a solvent choice would permit comparison with the very extensive data available for aminolysis of simple *p*-nitrophenyl esters,[3] we chose DMF as a solvent which is more likely to be employed by the practicing peptide chemist. Previous studies had indicated that aminolyses in this solvent show first-order rate behavior with respect to amine.[1] It may be noted that recent studies of the aminolysis of phenyl esters in nonaqueous solvents have argued strongly that collapse of a reversibly formed tetrahedral intermediate is rate determining[4] and have established the potent catalytic capacity of hydrogen bond acceptors.[5]

Several earlier studies have considered the effects of peptide substituents on rates of peptide forming aminolysis reactions. Using 2,4,5-trichlorophenyl esters, Pless and Boissonnas established the half-times for reactions of 17 activated amino acids with benzylamine in dioxane, as well as half-times for the reaction of the trichlorophenyl ester of ZPheOH with 13 amino acid esters.[6] In an investigation directly pertinent to the present study, Khurgin and Dmitrieva measured hydrolysis and aminolysis rate constants for the *p*-nitrophenyl esters of 11 carbobenzoxy amino acids and noted a correlation in the nonhindered cases with σ^* values.[7,8]

Results

To obtain data to test the validity of eq 1, 30 rate constants were measured for the reactions of the *p*-nitrophenyl esters of carbobenzoxy derivatives of Gly, Ala, Leu, Pro, Val, and Phe with the ethyl esters of the first five of these amino aicds. Although this series does not provide examples of large inductive effects or special side-chain reactivity, it does span nearly all of the range of steric effects to be encountered in peptide synthesis, and it is expected that steric effects should provide the most interesting test cases for eq 1. Reactions were carried out in dimethylformamide at 30° under pseudo-first-order conditions at *ca.* 10^{-4} *M* active ester concentration, with at least a fourfold range of amine concentrations, between 0.002 and 0.1 *M*. Linear de-

Table I
Rate Constants for *p*-Nitrophenyl Ester Coupling Reactions in DMF

1. Z—A—O-*p*-NPh + H—B—OEt $\xrightarrow[30°]{DMF}$ HO-*p*-NPh + Z—A—B—OEt

A[a]	B[a]	k_2, M^{-1} min^{-1} [b]	k_2(calcd)[c]
Gly (1738-86-9)[d]	Gly (459-73-4)	26.3 (0.3)	
Ala (1168-87-2)	Gly	16.7 (1.2)	
Val (10512-93-3)	Gly	1.28 (0.01) 1.11 (0.07)	
Leu (1738-87-0)	Gly	11.2 (0.2) 11.2 (0.01)	
Pro (3304-59-4)	Gly	9.05 (0.1)	
Phe (2578-84-9)	Gly	14.1 (0.3)	
Asn (3256-57-3)	Gly	7.2 (0.3)	
Gly	Ala (3082-75-5)	6.06 (0.2)	
Ala	Ala	4.4 (0.2)	3.7
Val	Ala	0.26 (0.03)	0.28
Leu	Ala	2.16 (0.04)	2.5
Pro	Ala	1.31 (0.02)	2.0
Phe	Ala	2.5 (0.1)	3.1
Gly	Val (17431-03-7)	2.06 (0.02)	
Ala	Val	1.21 (0.04)	1.3
Val	Val	0.062 (0.002)	0.099
Leu	Val	0.56 (0.02)	0.88
Pro	Val	0.43 (0.05)	0.71
Phe	Val	0.62 (0.02)	1.10
Gly	Leu (2743-60-4)	2.84 (0.01)	
Ala	Leu	1.9 (0.1)	1.8
Val	Leu	0.119 (0.005)	0.14
Leu	Leu	1.05 (0.01)	1.2
Pro	Leu	0.670 (0.006)	0.97
Phe	Leu	1.3 (0.2)	1.5
Gly	Pro (5817-26-5)	6.87 (0.05)	
Ala	Pro	1.63 (0.02)	4.4
Val	Pro	0.155 (0.003)	0.33
Leu	Pro	0.51 (0.07)	3.0
Pro	Pro	0.135 (0.005)	2.4
Phe	Pro	1.39 (0.01)	
Gly	Phe (3081-24-1)	1.00 (0.02)	
Phe	Phe	0.46 (0.04)	0.54

2. X—A—O-*p*-NPh + H—B—O—Y $\xrightarrow[30°]{DMF}$ HO-*p*-NPh + XA—B—O—Y

X-A[a]	HB—O—Y[a]	k_2, M^{-1} min^{-1}	k_2(calcd)
BOCGly (3655-05-8)	GlyOEt	23.1 (0.2)	
BOCGly	AlaOEt	5.8 (0.3)	5.1
BOCLeu (3350-19-4)	GlyOEt	9.7 (0.1)	
BOCLeu	AlaOEt	1.9 (0.2)	2.1
ZGly	AlaO-*t*-Bu (15911-69-0)	8.43 (0.2)	
ZGly	LeuO-*t*-Bu (21691-53-2)	4.86 (0.05)	
ZAla	AlaO-*t*-Bu	6.7 (0.1)	5.4
ZAla	LeuO-*t*-Bu	3.5 (0.2)	3.1

[a] All amino acids have the L configuration. [b] The term in parentheses is the least-squares error in slope. [c] k_2(calcd) is obtained by applying eq 1 to the experimental rate constants observed for glycine couplings [d] Registry no. are in parentheses below compounds.

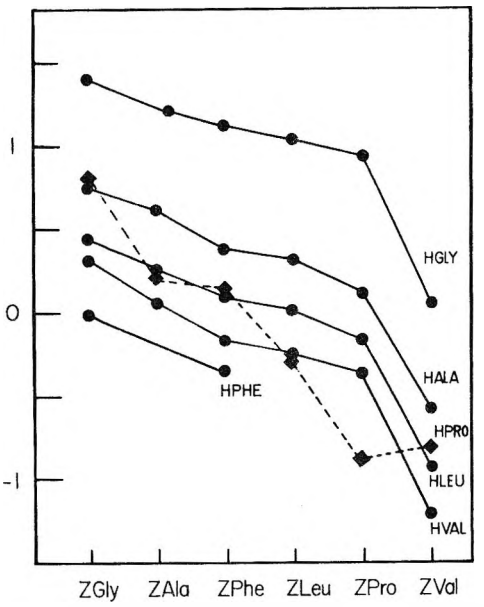


Figure 1. Log k_2, logs of second-order rate constants for coupling reactions of carbobenzoxyamino acid *p*-nitrophenyl esters with amino acid ethyl esters; data from Table I.

pendence of pseudo-first-order rate constant on amino concentration was noted in all cases, implying that the rates of these reactions are simply dependent on the products of amine and active ester concentrations. Data are presented in Table I.

Also included in the Table are comparisons of relative reactivities of Gly, Leu, and Ala derivatives bearing other blocking groups. In accord with the findings of Pless and Boissonnas,[6] the *tert*-butoxycarbonyl and benzyloxycarbonyl amino acid esters are found to be nearly identical in reactivity. A surprising finding is the significantly greater reactivity of the *tert*-butyl over the ethyl esters of Ala and Leu. A competition experiment was carried out in which equivalent amounts of HLeuOEt and HLeuO-*t*-Bu were allowed to react with the *p*-nitrophenyl ester of ZGlyOH in DMF. Cleavage of the neutral product mixture with trifluoroacetic acid gave ZGlyLeuOH in significant excess of the ZGlyLeuOEt formed, demonstrating that the effect is in fact real, and not an artifactive error of the kinetic procedure. Cases in which a more hindered derivative is more reactive are usually argued to arise from a relief of steric strain at the transition state, or from attractive London forces in a presumably polarizable transition state. It is difficult to argue for the former explanation in the case at hand.

Accompanying each entry of the table is an error estimate and a rate constant calculated from eq 1. It may be seen that with the exception of reactions of HProOEt, the success of the approximation is very good, and it may be noted that a still better fit would be possible by adjusting the partial rate factors for each amino acid. We have not chosen to do so, since the deviations from the present approximation should provide a measure of direct or indirect substituent–substituent interactions for the coupling transitions state.

A more obvious means of noting the magnitude of the proline anomaly is seen by the graph of Figure 1 which plots log k_2 for families of amino acids. The log of a rate constant which obeys eq 1 should be a simple sum of logs of partial rate factors, and families of such rate constants should show a simple additive increase or decrease as one amino acid is changed. As may be noted from the figure, exactly this behavior is observed for all amines but

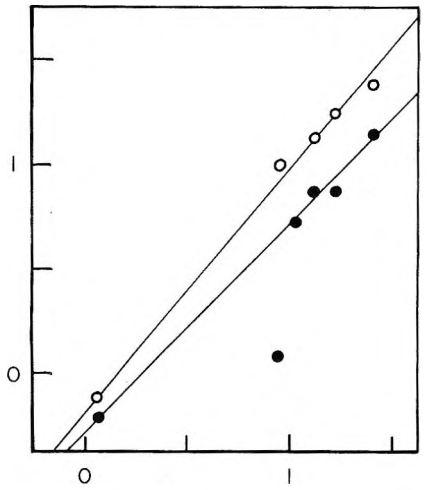


Figure 2. Open circles: logs of coupling rate constants for reaction of amino acid 2,4,5-trichlorophenyl esters with benzylamine in dioxane plotted against log k_2 for the corresponding reaction of a *p*-nitrophenyl ester with ethyl glycinate in DMF (ref 6). Closed circles: corresponding plot of log k_2 for reaction of the *p*-nitrophenyl ester with glycylglycine in water (ref 8).

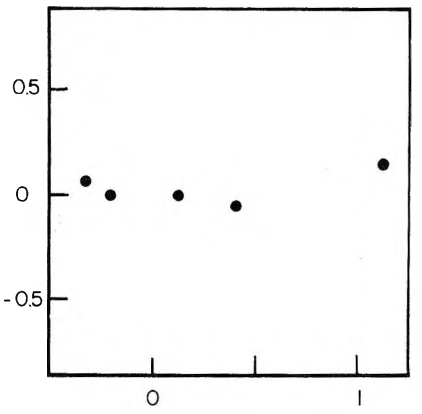


Figure 3. Log k_2 for the reaction of ZPhe trichlorophenyl ester in dioxane with amino acid methyl esters as functions of log k_2 for the reaction of ZPhe *p*-nitrophenyl ester in DMF with the corresponding amino acid ethyl esters (ref 6).

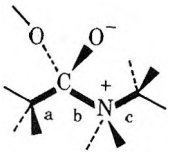
HProOEt. A statistical analysis is best applied to log k_2 values; the mean deviation of the 15 values which can be approximated by eq 1 is +0.052, the values ranging from −0.09 to +0.13. For the five HProOEt data, the mean deviation is +0.41, with a range of +0.09 to +0.94.[9] Clearly proline esters, unlike the other nucleophiles, show coupling rate constants which are very sensitive to interaction effects with substituents on the electrophilic partner.

Figure 1 also demonstrates an interesting, highly regular feature of these data. Whereas the substitution of a Val for a Gly causes a large rate change at both the C and N sites [av log (k_{Gly}/k_{Val}) = 1.40 (0.08) at C, 1.23 (0.09) at N], the substitution of Ala, or Leu for Gly causes a much larger rate change at the N than at the C site [*e.g.*, av log (k_{Gly}/k_{Ala}) = 0.18 (0.04) at C, 0.70 (0.09) at N].

Although the data of earlier workers are not extensive enough to permit test of eq 1, it is nonetheless interesting to compare where possible the effects of steric factors on rate constants as observed here for aminolysis of *p*-nitrophenyl esters in DMF with data observed for other solvents and esters. Figure 2 shows a log–log plot of the second-order rate constants observed by Pless and Boissonnas[6] for the reactions of 2,4,5-trichlorophenyl esters with benzylamine in dioxane as functions of the rate constants reported in Table I with ethyl glycinate as nucleophile. Also included is a similar plot of the data of Khurgin and Dmitrieva[8] for reactions of *p*-nitrophenyl esters with glycylglycine in water. Though the comparison data are not abundant, there appears to be a good linear correlation with nearly unit slope for rate constants resulting from structural changes of the active ester. It would therefore appear that similar steric effects attend phenolic ester couplings involving differing solvent or ester substitutions. Strikingly, the trichlorophenyl ester data imply that the opposite conclusion must be drawn for structural changes with the amine, for Figure 3 indicates that no significant correlation exists between the rate variations with amine substitution for reactions with 2,4,5-trichlorophenyl esters in dioxane and *p*-nitrophenyl esters in DMF.

Discussion

A theory or model which is proposed to rationalize the above observations must contend with several formidable uncertainties. Aminolysis of an ester involves three major bond changes at the reaction site—a C–N amide bond is formed, C–O ester and N–H amine bonds are broken. Although the precise timing of these events remains obscure despite much careful investigation,[10] it is likely that the rate-determining transition state bears substantially tetrahedral substitution at both the acyl carbon and amide nitrogen atoms, and the solvent is coordinated with both the NH_2^+ and O–C–O–X regions. In principle, three rotamers are possible at each of three single bonds, resulting in 27 potential conformations for the rate-determining transition state.[11] A new center of asymmetry at the acyl carbon is unique to the transition state. (Although there is doubtless a preferred chirality at this center, none of the subsequent analysis of *p*-nitrophenyl ester results appears to offer insight into this preference, and in the ensuing discussion we



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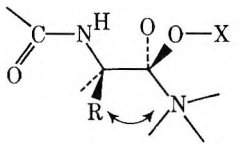
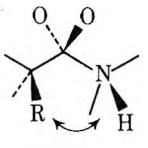
ignore it.) Clearly in a situation of this complexity, with relatively few incisive experimental findings, rigorous theories are uncalled for and at best one can hope to propose a plausible model which has heuristic value for new experiments. The model which is developed in the following discussion has proved very useful to us in rationalizing and predicting steric effects for a variety of intramolecular aminolysis reactions encountered during exploratory research with new types of peptide coupling reactions,[12] and for this reason, is developed here in etail.

Two general, preliminary points may be noted. First, it appears that the variations in rate constants observed in this study do reflect steric effects peculiar to the transition state, since what information is available implies that product stability shows a very different substituent pattern.[13] Second, there is more than adequate precedent in the quantitative behavior of other crowded systems to explain the range of effects observed in this study. To develop this point, one can note that two kinds of changes occur which affect the environment of a substituent R, attached at the carbon α to the acyl site as the *p*-nitrophenyl ester is converted into the transition state for aminolysis; first, a staggered 1,2 interaction is created between the R and acyl amino groups and the O or N atoms of the acyl carbon; second, a 1,3 interaction is created between the R or acylamino groups and the N–H functionality of the nucleophile.

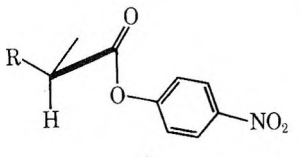


1,2 interaction

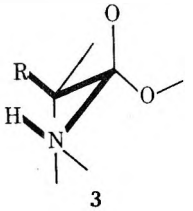


1,3 interaction

Despite the uncertainties in bond distances and structural features, one can find in the axial–equatorial energy differences for monosubstituted chair cyclohexanes a rough analogy for the new 1,3 interaction resulting from the conversion of **2** into **3**. For our aminolyses the change in free ener-



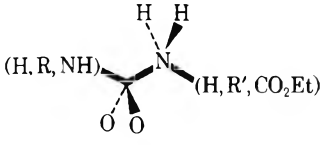
2



3

gy of activation, $\Delta(\Delta G^*)$, for the substitution of R = CH_3 for R = H is 0.25 kcal/mol, while that for the substitution of *i*-Pr for H is 1.9 kcal/mol. These may be compared with *A* values for Me and *i*-Pr of roughly 1.3 and 2.1 kcal/mol.[14,15] For substitution at the site α to the amino nucleophile, a change from R = H to R = Me leads to $\Delta(\Delta G^*)$ of 0.97 kcal/mol, which may be compared with an a–e interaction energy difference for *cis*-3-hydroxymethylcyclohexane of 2.1 kcal/mol.[15] Thus it is likely that even considering only 1,3 interactions, no special factors need be invoked to explain the magnitude of the rate differences seen in this study.

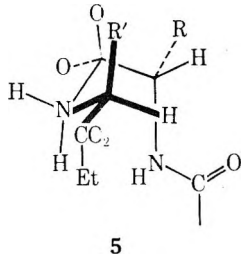
The peculiarities of the rate data which a model might seek to explain include (1) the success of eq 1 in predicting rate constants for most coupling reactions; (2) the failure of eq 1 for prediction of rate constants for reactions involving HProOEt; and (3) the differing magnitudes of substituent effects at C and N termini. In developing the model, we



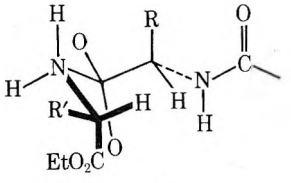
4

employ fact 3 to select among the conformational choices and show that the resulting conformations of lower energy lead to a prediction of facts 1 and 2.

Many of the 27 conformations of **1** can be readily seen to be impossibly crowded; inspection of the subclasses of anti and gauche rotamers about the developing C–N bond (bond b of **1**) allows the most simple analysis of this fact. Thus, the anti rotamer, **4**, allows minimal interaction be-



5



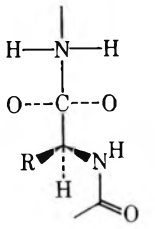
6

tween the bulky ends, and all nine conformers which maintain this anti relationship are therefore expected to be sufficiently close in energy to require more information before a stability ranking can be proposed for them. In contrast, the gauche C–N rotamers have very severe end group interactions unless the two proximate terminal groups are both hydrogens, as indicated in **5** and **6**. Although as will be seen, either **5** or **6** appears to be more crowded than the average of the nine anti C–N cases, the energy difference is probably small enough that **5** and **6** must be considered as possible contributors to product formation. There are thus 11 serious candidates for the conformations of the product forming transition state.

As the above structures indicate, in none of the 11 is a *direct* R–R′ interaction possible, and therefore *the conclusion that* **4**, **5**, *and* **6** *are sterically favored also establishes the molecular basis for the validity of equation 1 for the nonproline nucleophiles.*

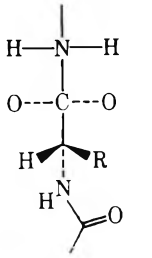
Explanation of the proline anomaly now rests on the results of an analysis of conformational preferences about the a and c bonds of the anti N–C conformation, **4**, and a consideration of **5** and **6**.

The C–C bond a of **1** has three possible rotamers, **7**, **8**, and **9**, which must differ in energy to the degree that the indicated pairs of interactions are different.[16]



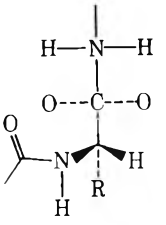
1,3 NH—amido
1,3 NH—R

7



1,3 NH—R
1,2 O—amido

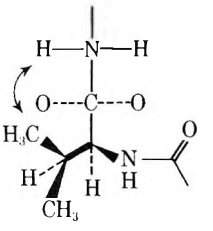
8



1,3 NH—amido
1,2 O—R

9

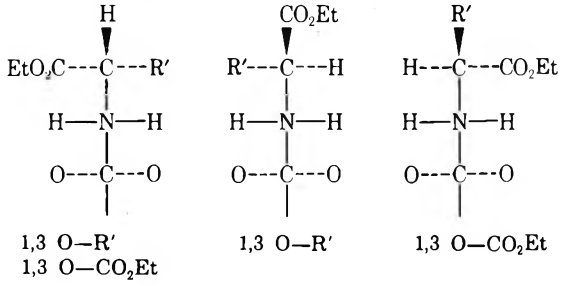
The three rotamers thus have two kinds of interactions involving alkyl or amido groups: 1,2 interactions with oxygen functions at the acyl carbon, and 1,3 interactions with hydrogens at the amino nitrogen. An *a priori* evaluation of the magnitude of these interactions is not possible, since the C–N bond b is likely of abnormal length, and the steric environment at the N–H and C–O sites may be altered by the presence of DMF molecules (the large solvent rate acceleration for this reaction should be recalled). However, the following argument can be based on the relative magnitude of the substituent effects. Of the two types of interactions, the 1,2-oxy interactions are expected to be large for both Me and *i*-Pr, while the 1,3-NH interaction must be large for *i*-Pr, but could be relatively small for Me if the N–C amide bond is long in the transition state. The observed change in free energy of activation with substitution at the acyl site is only 0.24 kcal/mol for H → Me, but becomes 1.8 kcal/mol for H → *i*-Pr. This pattern, therefore, supports the assertion that in the low energy rotamer, a large 1,2-oxy interaction is avoided, and the dominant energy change results from 1,3 interactions between the HN functions and amido or R groups. The rotamer **7** therefore appears to be the more stable if R ≠ H, and **7** and **9** must be the preferred rotamers for Gly (R = H). Avoidance of an overriding 1,2-oxy interaction presumably favors one rotamer of the three at the α–β alkyl bond of valine and thus forces this case (R = *i*-Pr) into conformation **10**, which has a significant 1,3 interaction.



10

The model predicts that substituents at the amino site must encounter an opposite interaction pattern. The 1,2 interaction now occurs between an alkyl group and N–H hydrogens and is expected to be small, while the 1,3 interactions between acyl C–O and alkyl or ester functions must be large.

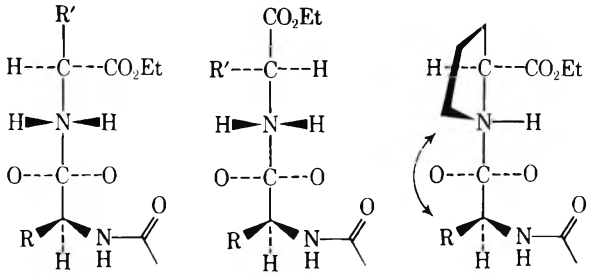
Unique among the amino acids, glycine can assume conformation **12**, R = H, which has no significant 1,3 interactions. All other amino acids are expected to assume conformations **12** and **13**, R ≠ H, which have only one 1,3 interac-



11 **12** **13**

tion of importance. The unusual, large rate constants for HGlyOEt are thus understandable. [For substitution at the amino site, $\Delta(\Delta G^*)$ = 0.9 kcal/mol for H → Me, and 1.5 kcal/mol for H → *i*-Pr.]

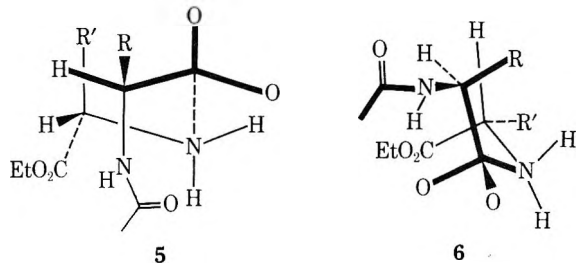
In **14** and **15** are summarized the overall structural features proposed by the model for the lowest energy conformers of the aminolysis transition state. From these the pro-



14 **15** **16**

line anomaly is readily rationalizable, for with HProOEt as a nucleophile, **14** necessarily becomes **16**, which now bears a new alkyl–alkyl interaction between R and the proline side chain resulting in direct steric interactions between the peptide substituents, and as a result, eq 1 cannot be obeyed. An equivalent deduction follows if the Pro side chain is considered as a part of **15**.

By a similar sort of analysis, one can show that for the two gauche conformations, **5** and **6**, the environment about



5 **6**

R in **5** has the 1,2 and 1,3 interactions of **9**, with an additional 1,3 interaction between bond and a C–H; similarly **6** is expected to be more crowded than **8**. A similar, more hindered situation obtains at R′, and it seems reasonable, as noted earlier, that neither conformation represents a major path for the reaction. Both **5** and **6** predict obedience to eq 1, but neither can be used to explain the proline deviations. Moreover, of the 9 rotamers theoretically possible at the a and c bonds of the trans N–C conformation, only two allow

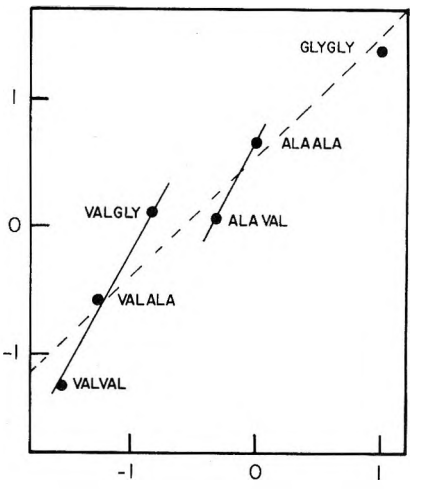


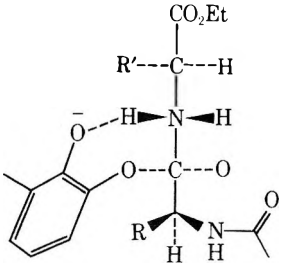
Figure 4. Log k_2 for the aminolysis reactions of esters of 2,3-dihydroxy-*N*-ethylbenzamide in DMSO as functions of log k_2 for the corresponding reaction of the *p*-nitrophenyl ester (ref 2).

the 1,3 R–C–C–N–X interaction which explains the proline result.

It is interesting to attempt to generalize the model to other phenyl ester aminolyses. The marked insensitivity of the 2,4,5-trichlorophenyl ester rates to the steric environment of the amino component was noted above and would appear to require a very different steric situation at the amino but not the acyl side of the transition state. Possibilities include a longer C · · · O-ϕ bond, and attractive dispersion interactions between the ortho chlorine atom and the R or carboethoxyl groups. Similar halogen interactions must be invoked in simple acyclic systems to explain conformational preferences.[18] More information is needed before the intriguing features of this system can be placed in their proper perspective.

A second case of interest is provided by the aminolysis reactions of the 3-acyloxy-2-hydroxy-*N*-ethylbenzamides, which display a very similar steric pattern at both acyl and amino sites to that seen in this study for *p*-nitrophenyl esters,[2] and which appear on the basis of limited data to yield rate constants which obey eq 1.

Moreover, as indicated by Figure 4, the pattern of effects is similar to that found in the present study, although a somewhat greater sensitivity to acyl substitution, R, and a lesser sensitivity to R′ may be noted. Further evidence strongly supports a mechanism in which internal proton transfer or hydrogen bonding to the catechol monoanion occurs in the rate-determining transition state.[2] The above anti N–C model can be adapted to accommodate this special feature, and **17** or its acyl epimer is the result.

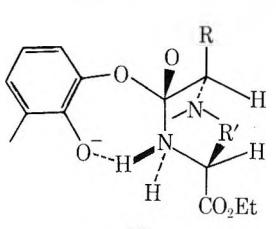


17

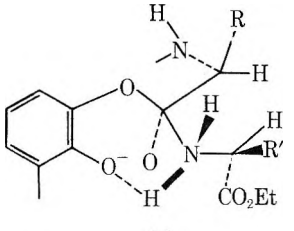
Molecular models imply that the introduction of the catechol ester functionality significantly increases the crowding of one quadrant of **17**, although even approximate molecular analogies which would allow energy estimates for this environment are problematic. Since the catechol environment of **17** is remote from R or R′, increased crowding

by the catechol need not increase the steric effects of rendering R and R′ bulky, and greater hindrance of **17** over **14** or **15** is therefore not inconsistent with the similar spans of rate constants for the catechol and *p*-nitrophenyl esters. However, the experimental finding that $HProO^-$ reacts more than a hundred times more slowly than expected with 3-carbobenzoxyglycyloxy-2-hydroxy-*N*-ethylbenzamide appears to be inexplicable in terms of the model **17** or its acyl epimer. The magnitude of this rate discrepancy is such that it is likely that no hydrogen bonding occurs between the catechol oxy anion and the single proline NH at the transition state. The acyl epimer of **17**, which allows hydrogen bonding, is therefore excluded, and the more hindered, nonhydrogen bonded **17** would have to be the energetically preferred conformer. This result is unreasonable since the asymmetry at the acyl carbon which positions the catechol must be induced by the asymmetry of the proline function, which is the only center of chirality in the starting materials; there appears to be no factor which can be invoked to override the energetically favorable hydrogen bond.

Consideration of structures **5** and **6** permits a consistent rationalization, for these structures allow the catechol oxy anion an uncrowded environment; thus **5** becomes **18**; and **6**, **19**. Structure **18** cannot accommodate a proline methylene substitution, while **19** can only do so at the expense of a severe 1,3-dialkyl interaction which is augmented by a buttressing effect of the 1,3-O—CO_2Et interaction on the opposite side of the molecule.



18



19

Summary

Models have been discussed which while admittedly speculative, appear to account for the gross features and at least approximately, for the details of steric effects on rates of aminolyses of peptide phenyl esters by peptide amines. The major experimental finding of obedience to eq 1 requires an anti conformation about the forming C–N bond or one of two gauche conformations in which the conformations about the remaining bonds are fixes as in **5** or **6**. These rotamers can be independently assigned as the less hindered among the 27 possibilities. For the *p*-nitrophenyl ester case, the proline deviations and the differing pattern of steric effects for acyl and amine substituents are consistent with only two among the anti C–N rotamers as providing the major reaction pathway.

More data are needed with other phenyl esters before general conclusions can be drawn, but we stress that the present model, however crude and speculative, provides a first step toward a predictive scheme for substituent effects on peptide bond forming reactions. In subsequent discussions we will describe application of this model to rationalizing the strikingly different substituent rate effects which arise when the peptide bond forming aminolysis reaction is made intramolecular.

Experimental Section

Unless otherwise specified, reagents and solvents were reagent grade; amino acids were Calbiochem A grade. Carbobenzoxyamino acids[19] were prepared by literature procedures and were recrystallized to constant melting point, or converted into their dicyclohexylamine salts and purified to constant melting point. The *p*-nitrophenyl esters[19] of N-protected amino acids were prepared using dicyclohexylcarbodiimide and *p*-nitrophenol, following the procedure of Bodanszky and duVigneaud;[20] ethyl acetate was used as solvent except for ZAsnOH, for which DMF was substituted. Amino acid ethyl ester hydrochlorides were prepared by the Boissonnas modification[21] of Fischer esterification and were recrystallized to literature melting point. DMF for kinetic runs was obtained by distilling a 3:1 mixture of reagent grade DMF and toluene at 30 mm through a 55-cm spinning band column. The middle DMF fraction was collected, sealed, and stored in a desiccator over P_2O_5–KOH. Optical rotations were measured in a 1-dm microcell, using a Perkin-Elmer Model 141 polarimeter.

Product Determination. For most reactions studied, products were isolated in at least 80% yield and characterized from reactions in DMF at 0.05 *M* reagent concentrations. The Z-protected ethyl esters of the following dipeptides were characterized by comparison of melting point and in most cases $[\alpha]_D$ with literature values: GlyGly, AlaGly, ValGly, LeuGly, GlyAla, AlaAla, ValAla, LeuAla, PheAla, AsnAla, ValVal, ValLeu, and LeuLeu. The following dipeptides were characterized as hydrazides, obtained by hydrazinolysis of the ethyl esters: ProGly, GlyVal, LeuVal, ProVal, GlyLeu, AlaLeu, ProLeu. The dipeptides with C-terminal proline residues were isolated in high yield as oils. The following new substances were prepared by the above coupling procedure and characterized.

Ethyl *tert*-Butoxycarbonyl-L-leucylglycinate. Needles from ether–petroleum ether: mp 83–84°, $[\alpha]^{22}_D$ −25.8 (1.6, EtOH). *Anal.* Calcd for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.98; H, 8.98; N, 8.90.

Benzyloxycarbonyl-L-prolyl-L-alanine Hydrazide. Crystals from ethanol–ether: mp 142–143°, $[\alpha]^{22}_D$ −12.7 (0.5, EtOH). *Anal.* Calcd for $C_{26}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.69; H, 6.66; N, 16.20.

Ethyl Benzyloxycarbonyl-L-asparaginyl-L-alaninate. Needles from ethanol–ether: mp 183–184°, $[\alpha]^{22}_D$ −38.2 (0.2, DMF). *Anal.* Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.35; N, 11.50. Found: C, 55.79; H, 6.44; N, 11.47.

Ethyl *tert*-Butoxycarbonyl-L-leucyl-L-alaninate. Needles from ether–petroleum ether: mp 111–112°, $[\alpha[^{22}_D$ −40.2 (1.0, EtOH). *Anal.* Calcd for $C_{16}H_{30}N_2O_5$: C, 58.16; H, 9.15; N, 8.48. Found: C, 58.13; H, 9.02; N, 8.44.

Ethyl Benzyloxycarbonyl-L-alanyl-L-valinate. Needles from ethyl acetate–petroleum ether: mp 82–83, $[\alpha]^{22}_D$ −29.9 (1.1, EtOH). *Anal.* Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 8.00. Found: C, 61.89; H, 7.50; N, 8.00.

Kinetic Procedure. Within 2 days of a kinetic run, samples of amino acid ethyl or *tert*-butyl esters were liberated from their salts with 33% NaOH solution, extracted, dried over K_2CO_3, and distilled *in vacuo*, then stored at 0° until immediately before use. Ethyl glycinate was distilled before use. For rate measurements, stock solutions of amino acid ethyl or *tert*-butyl esters (0.1–0.3 *M*) and N-blocked amino acid *p*-nitrophenyl ester (*ca.* 10^{-3} *M*) were prepared in dry DMF. Volumes of amine stock solution were pipetted into four 25-ml volumetric flasks which were filled to 23 ml with DMF and brought to 30°. To initiate a run, 1.0 ml of *p*-nitrophenyl ester solution was added to the flask, which was filled with DMF to the mark, and the resulting solution was mixed and transferred to a 1-cm silica cuvette. Absorbance measurements were made at 325 nm in a Zeiss PMQ II spectrophotometer, equipped with a thermostated cell block maintained at 30 ± 0.1° and connected to a Hewlett-Packard 3440-3A digital voltmeter and H03571B-562A digital printer. Reactions were conducted at 0.003 to 0.1 *M* amine concentrations; in almost all cases four concentrations in the range 0.01 to 0.05 *M* were chosen. Reactions were followed to 2 to 2.5 half-lives, and infinity points were taken at 10 half-lives. Pseudo-first-order rate constants were obtained for each run at fixed amine concentration by a linear least-squares analysis of $\ln (A_\infty - A_t)$ *vs. t*. Second-order rate constants were obtained by a linear least-squares analysis of pseudo-first-order rate constants for reactions at different amine concentrations; in nearly all cases, four concentrations were used, but in two or three instances, five or three were employed. A value of 10% of the smallest pseudo-first-order rate constant was observed for the average zero intercept term, which presumably is attributable in part to aminolysis by traces of dimethylamine in the solvent.

Acknowledgment. Financial support from National Institutes of Health Grant GM 13453 is gratefully acknowledged.

Registry No.—Ethyl *tert*-butoxycarbonyl-L-leucylglycinate, 51220-76-9; benzyloxycarbonyl-L-prolyl-L-alanine hydrazide, 52895-37-1; ethyl benzyloxycarbonyl-L-asparaginyl-L-alaninate, 52928-60-6; ethyl *tert*-butoxycarbonyl-L-leucyl-L-alaninate, 52895-38-2; ethyl benzyloxycarbonyl-L-alanyl-L-valinate, 52895-36-0.

References and Notes

(1) A preliminary report of these results was presented in "Peptides 1971," H. Nesvadba, Ed., North-Holland, Amsterdam, 1973, p 7.
(2) D. Kemp, S-W. Wang, J. Rebek, Jr., R. Mollan, C. Banquer, and G. Subramanyam, *Tetrahedron*, in press.
(3) For a review, see S. L. Johnson in "Advances in Physical Organic Chemistry," Vol. 5, V. Gold, Ed., Academic Press, New York, N.Y., 1967, p 237.
(4) F. M. Menger and J. H. Smith, *J. Amer. Chem. Soc.*, **94**, 3824 (1972).
(5) C. Su and J. W. Watson, *J. Amer. Chem. Soc.*, **96**, 1854 (1974).
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(8) Yu. I. Khurgin and M. G. Dmitrieva, *Tetrahedron*, **21**, 2305 (1965).
(9) Student's tests, when applied to the proline and nonproline cases, establish that the two populations are distinct with a certainty considerably beyond the 99% confidence level.
(10) See discussion and references in ref 3, 4, and 5; also A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5442 (1970), and W. P. Jencks, *ibid.*, **94**, 4733 (1972).
(11) For a rigorous approach to a problem of this kind, see E. Ruch and I. Ugi in "Topics in Stereochemistry," Vol. 4., E. Eliel and N. Allinger, Ed., Wiley-Interscience, New York, N.Y., 1969, p 105.
(12) D. S. Kemp and F. Vellaccio, unpublished observations.
(13) For example, valyl and isoleucyl peptides are known to hydrolyze more slowly than average, and heats of hydrolysis, though varying significantly, do not appear to reflect simple steric trends. Pertinent references include R. L. Hill in *Advan. Protein Chem.*, **20**, 37 (1965); M. Rawitscher, I. Wadsö, and J. M. Sturtevant, *J. Amer. Chem. Soc.*, **83**, 3180 (1961); and J. P. Greenstein and M. Winitz, "The Chemistry of the Amino Acids," Vol. 1, Wiley, New York, N.Y., 1961, pp 558 ff.
(14) J. A. Hirsch in "Topics in Stereochemistry," N. Allinger and E. Eliel, Ed., Interscience, New York, N.Y., Vol. 1.
(15) E. Eliel, N. Allinger, S. Angyal, and G. Morrison, "Conformational Analysis," Interscience, New York, N.Y., 1965, pp 44–66.
(16) Each of the conformers **7**, **8**, and **9**, has six pertinent interactions; however, three of these occur identically, and in each case an additional interaction involves the α-H and is expected to be small. The remaining two are listed below the structures.
(17) Models suggest that this 1,3 alkyl–alkyl interaction should be most severe when both alkyl functions are relatively rigid, as is the case when both are derived from proline side chains; it may be noted that the deviation from eq 1 in the Pro-Pro case is very large.
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Carbon-13 Nuclear Magnetic Resonance Spectra of Branched-Chain Sugars. Configurational Assignment of the Branching Carbon Atom of Methyl Branched-Chain Sugars[1]

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Carbon-13 nmr spectra of α and β anomers of branched-chain sugars, having the branched-chain group (methyl) at the 2 and 4 carbons and epimeric at the branching carbon atom, are reported and discussed.

The identification of a relatively large number of branched-chain sugars as the glycoside component of antibiotics,[2] the discovery that cell walls of some aquatic plants contain a high percentage of the branched-chain sugar apiose,[3] the isolation of branched-chain sugar nucleotides from the microorganism *Azobacter vinelandi*,[4] and the observed cytostatic and virostatic activity of nucleosides with branched-chain sugars[5–7] are all responsible for the rapid development of the synthetic chemistry of branched-chain sugars in recent years.

However, the determination of the configuration of a branching carbon atom in branched-chain sugars was notoriously difficult, since a simple and reliable method was not available.[8]

In late 1972 carbon-13 nmr spectroscopy was applied, for the first time, to the configurational assignment of quaternary carbon atoms in branched-chain sugars having the 1,3-dithian-2-yl and 2-methyl-1,3-dithian-2-yl residues as the branched chains.[20–23]

Using the observation on methylcyclohexanes[24,25] that the carbon-13 chemical shift of an axial methyl group is ~6 ppm upfield relative to that of an equatorial methyl group, we have unequivocally determined the configuration of the branching-carbon atom in a number of branched-chain sugars having the branched chain (methyl group) at the 4-carbon atom.[26] Since the influence of the configuration of the branching-carbon atom and the anomeric configuration upon the carbon-13 resonances of other carbon atoms of a branched-chain sugar was not thus far studied and since the methyl group is the most frequent branched chain in naturally occurring branched-chain sugars, a detailed analysis of carbon-13 nmr spectra of α and β forms of branched-chain sugars epimeric at the branching carbon atom seemed appropriate. The following branched-chain sugars were studied by carbon-13 nmr spectroscopy: methyl 4-*C*-methyl-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**1**), methyl 4-*C*-methyl-3-*O*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**2**), methyl 4-*C*-methyl-2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (**3**), methyl 4-*C*-methyl-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**4**), methyl 4-*C*-methyl-3-*O*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**5**), methyl 4-*C*-methyl-2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (**6**), methyl 4-*C*-methyl-2,3-di-*O*-methyl-6-*O*-triphenylmethyl-β-D-galactopyranoside (**7**), methyl 4-*C*-methyl-2,3-di-*O*-methyl-6-*O*-triphenylmethyl-β-D-glucopyranoside (**8**), methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-3-*O*-methyl-α-D-glucopyranoside (**9**), methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-3-*O*-meth-

Table I

Line	Branched-chain sugar, chemical shifts[a]										Assignment
	1	2	3	4	5	6	7	8	9	10	11	
1	99.5	98.1 DQ[b]	97.7 DQ	98.9	97.6	97.4 DQ	104.9 DQ	105.2 DQ	102.6	104.2	103.8 DQ	C-1
2	70.7	79.1 DQ	80.0 DQ	71.1	78.9	80.9 DQ	82.9 DQ	83.1 DQ	41.3	37.6	38.1 DQ	C-2
3	84.3	81.0 DQ	83.0 DQ	86.0	82.4	85.1 DQ	86.8 DQ	88.4 DQ	80.1	76.6	79.5 DQ	C-3
4	73.8	74.9 ST[b]	74.2 ST	74.7	75.9	74.4 ST	73.6 ST	74.7 ST	84.4	79.1	78.9 DQ	C-4
5	73.2	72.5 DQ	72.9 DQ	71.5	70.7	71.2 DQ	77.7 DQ	75.6 DQ	63.0	63.8	67.6 DQ	C-5
6	63.1	63.1 ST	63.4 ST	63.1	63.0	63.1 ST	63.4 ST	63.2 ST	69.4	69.1	68.9 ST	C-6
7	55.1	55.4 DQ	55.3 DQ	55.2	55.4	55.1 DQ	56.7 DQ	57.1 DQ	55.0	54.7	56.9 DQ	C-1 CH_3O
8			58.9 DQ			58.9 DQ	60.7 DQ	60.6 DQ				C-2 CH_3O
9		37.7 DQ			38.2							C-2 CH_3SO_3
10									12.4	11.0	5.7 DQ	C-2 CH_3
11	62.2	62.2 DQ	62.1 DQ	61.9	61.7	61.9 DQ	62.2 DQ	61.9 DQ	60.8	57.7	57.6 DQ	C-3 CH_3O
12	21.9	21.7 DQ	21.8 DQ	15.4	15.3	15.6 DQ	21.3 DQ	16.0 DQ				C-4 CH_3
13	87.2	87.5 ST	87.4 ST	87.8	88.1	87.7 ST	87.5 ST	87.9 ST	101.4	101.8	101.7 DQ	C-O Ph
14	144.0	143.7 ST	144.2 ST	143.6	143.4	143.7 ST	144.2 ST	143.6 ST	137.8	137.8	137.7 ST	C-substituted Ph
15	127.8	127.9 DQ	128.0 DQ	128.0	128.1	128.0 DQ	128.1 DQ	128.2 DQ	128.2	128.1	128.1 DQ	C-ortho Ph
16	128.7	128.7 DQ	128.9 DQ	128.6	128.6	128.7 DQ	129.0 DQ	128.8 DQ	128.8	128.8	128.8 DQ	C-meta Ph
17	127.0	127.2 DQ	127.2 DQ	127.3	127.4	127.2 DQ	127.4 DQ	127.4 DQ	126.1	126.3	126.2 DQ	C-para Ph

[a] δ_C using internal tetramethylsilane as reference. [b] ST = singlet or triplet, DQ = doublet or quartet.[28]

yl-α-D-mannopyranoside (**10**), and methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-3-*O*-methyl-β-D-mannopyranoside (**11**).

The synthesis of branched-chain sugars **1–8** is already described,[26] whereas the preparation of branched-chain sugars **9–11** will be reported elsewhere.[27]

Table I summarizes the chemical shifts, assignments, and line multiplicities (in some examples) from the proton noise decoupled and off resonance spectra.

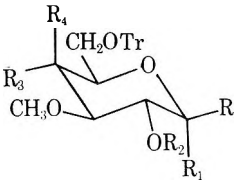
Lines 14–17 are assigned to aromatic carbon atoms of triphenylmethyl (branched-chain sugars **1–8**) and benzylidene (branched-chain sugars **9–11**) groups. The carbon-13 resonances of the C-substituted carbon of the benzene ring in branched-chain sugars **1–8** are low-field singlets at 143.6–144.2 ppm, whereas the carbon-13 resonances of the C-substituted carbon in branched-chain sugars **9–11** are the low-field singlets at ~137.8 ppm (line 14). The carbon-13 resonances of the *para* carbon of the benzene ring (line 17) are high-field doublets at 127.0–127.4 (for branched-chain sugars **1–8**) and at 126.1–126.3 (for branched-chain sugars **9–11**). Lines 15 and 16 are assigned to carbons in the ortho and meta position; these assignments can be, however, reversed.

The chemical shifts of the quaternary carbon atom of the triphenylmethyl group in branched-chain sugars **1–8**, and of the methine carbon of the benzylidene group in branched-chain sugars **9–11**, were determined on the basis of their position, consistency, and multiplicity (line 13). The carbon-13 resonances of the methine carbon in branched-chain sugars **9–11** (101.4–101.8 ppm) are in a very good agreement with the reported values in similar systems (100.9–101.6 ppm).[22] The carbon-13 resonances of the quaternary carbon of the triphenylmethyl group in branched-chain sugars **1–8** seem to be slightly influenced by the configuration of the 4-carbon atom. Thus, when the C-4 methyl group is equatorial (branched-chain sugars **1–3** and **7**) the carbon-13 resonances are 87.2–87.5 ppm, whereas in the corresponding C-4 epimers where the methyl group is axially oriented (branched-chain sugars **4–6** and **8**) the chemical shifts are 87.7–88.1 ppm.

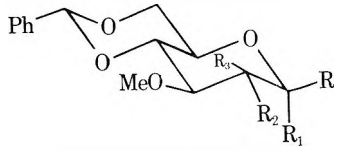
Line 7 is assigned to the C-1 methoxy group based on a previous finding[29] that the carbon-13 resonances of the C-1 methoxy group of α and β anomers are 55.12 and 56.70, respectively. The observed deshielding of the C-1 methoxy group in β anomers **7**, **8**, and **11** with respect to the corresponding α anomers **3**, **6**, and **10** (1.4–2.2 ppm) is in a good agreement with the reported value (1.5 ppm).[29]

The chemical shifts of the C-6 methylene carbons were determined on the basis of their position, multiplicity, and consistency (line 6). The carbon-13 resonances of the C-6 carbon of branched-chain sugars **1–8** (63.0–63.4 ppm) are in a good agreement with reported values (63.0–63.5 ppm),[30] whereas the chemical shifts of the C-6 carbon of branched-chain sugars **9–11** (68.9–69.4 ppm) are in a good agreement with values reported for 4,6-*O*-benzylidene derivatives of C-3 branched-chain sugars (68.8–69.0 ppm).[22] The chemical shifts of the C-6 carbon of branched-chain sugars **1–11** are independent of the anomeric configuration and seem to be not affected by the configuration of the branching-carbon atom and by the nature of substituents at other carbon atoms of the pyranoside ring.

Lines 8 and 11 are assigned to the C-2 and C-3 methoxy groups, respectively. The anomeric configuration should have larger effect upon the chemical shift of the C-2 methoxy group than upon the carbon-13 resonance of the C-3 methoxy group. The deshielding of the C-2 methoxy group in β anomers of branched-chain sugars **3**, **6**, **7**, and **8** is 1.8 ppm relative to the α anomers whereas it is insignificant for



1. R = R_2 = H; R_1 = CH_3O; R_3 = CH_3; R_4 = OH
2. R = H; R_1 = CH_3O; R_2 = CH_3SO_2; R_3 = CH_3; R_4 = OH
3. R = H; R_1 = CH_3O; R_2 = R_4 = CH_3; R_3 = OH
4. R = R_2 = H; R_1 = CH_3O; R_3 = OH; R_4 = CH_3
5. R = H; R_1 = CH_3O; R_2 = CH_3SO_2; R_3 = OH; R_4 = CH_3
6. R = H; R_1 = CH_3O; R_2 = R_4 = CH_3; R_3 = OH
7. R = CH_3O; R_1 = H; R_2 = R_3 = CH_3; R_4 = OH
8. R = CH_3O; R_1 = H; R_2 = R_4 = CH_3; R_3 = OH



9, R = R_3 = H; R_1 = CH_3O; R_2 = CH_3
10, R = R_2 = H; R_1 = CH_3O; R_3 = CH_3
11. R = CH_3O; R_1 = R_2 = H; R_3 = CH_3

the C-3 methoxy group. The C-4 methyl group orientation has, however, a small but definite influence upon the carbon-13 resonances of the C-3 methoxy group; *i.e.*, whenever the C-4 methyl group is axially oxiented the C-3 methoxy group is shielded by 0.2–0.3 ppm.

The carbon-13 resonances at 37.7 and 38.2 ppm in branched-chain sugars **2** and **5** are assigned to the methyl carbon of the C-2 methylsulfonyl group on the basis of their position and multiplicity (line 9).

Line 1 is assigned to the C-1 carbon since it is to the lowest field, excluding the aromatic carbons. The C-1 carbon of the β form of branched-chain sugars with the branching group at the C-4 carbon (branched-chain sugars **1–8**) is deshielded by 7.2 and 7.8 ppm with respect to the corresponding α anomer (**7** vs. **3** and **8** vs. **6**). The methylation or mesylation of the C-2 hydroxyl group causes an upfield shift of the carbon-13 resonance of the C-1 carbon atom. This shielding is larger when the C-2 hydroxyl group is methylated (1.3–1.8 ppm for **3** and **6**) rather than mesylated (1.3–1.4 ppm for **2** and **4**). The carbon-13 resonance of the anomeric carbon of branched-chain sugar **9**, where the C-2 methyl group is equatorially oriented, is shifted downfield by ~2 ppm with respect to methyl α-D-glucopyranoside,[30–32] whereas the C-1 carbon in branched-chain sugars **10** and **11**, where the C-2 methyl group is axially oriented, is deshielded by ~3 ppm with respect to methyl α- and β-D-mannopyranosides.[32] It has been reported[30,32] that the anomeric carbon of methyl α-D-mannopyranoside is deshielded by 1.0–1.4 ppm with respect to the anomeric carbon of methyl α-D-glucopyranoside. The similar amount of dishielding (1.6 ppm) is observed in branched-chain sugars **9** and **10**, which are 2-deoxy-2-methyl analogs of methyl α-D-gluco- and mannopyranosides. Furthermore, it has been reported[32] that the carbon-13 resonance of the anomeric carbon of methyl β-D-mannopyranoside is *shifted upfield* by 0.3 ppm with respect to the α anomer. The similar upfield shift (0.4 ppm) of the carbon-13 resonance of the C-1 carbon is observed in the β anomer (**11**) of branched-chain sugars **10** and **11**, which are 2-deoxy-2-methyl analogs of methyl α- and β-D-mannopyranosides.

The chemical shift of the C-2 carbon was determined on the basis of its position and multiplicity (line 2). For branched-chain sugars **1–8** there is a moderate downfield shift (~9 ppm) with methylation of the C-2 hydroxyl group which is in good agreement with the previous observation[31,33] that the methylation of a hydroxyl group causes an 8–11 ppm downfield shift in the position of the resonance of the directly attached carbon. The upfield position of the carbon-13 resonances of the C-2 carbon of branched-chain sugars **9–11** are due to the absence of a directly attached electronegative substituent, *i.e.*, hydroxyl group. From studies on methylated cyclohexanes[24] it is known[34] that an equatorially oriented methyl group deshields the carbon to which it is attached by 5.6 ppm whereas the carbon atom bearing an axially oriented methyl group is deshielded by 1.1 ppm. Subtracting the first value from the observed carbon-13 resonance of the C-2 carbon of branched-chain sugar **9** (41.3 ppm) and the second value from the observed carbon-13 resonances of the C-2 carbon of branched-chain sugars **10** and **11** (37.6 and 38.1 ppm), it can be calculated that the chemical shift of the C-2 carbon of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside would by 36.1–37.0 ppm. This calculated chemical shift is in a good agreement with reported values (35.8–36.4) for carbon-13 resonances of the C-2 carbon of 4,6-*O*-benzylidene-2-deoxy branched-chain sugars with a branching at the C-3 carbon atom.[22]

Lines 10 and 12 are assigned to C-2 and C-4 methyl carbons. In branched-chain sugars **1–6** (α anomers) the chemical shift difference between the equatorially and axially oriented C-4 methyl group is 6.4 ppm, whereas in branched-chain sugars **7** and **8** (β anomers) the chemical shift difference is 5.3 ppm. In both α and β anomers, the carbon-13 resonance of the axial C-4 methyl group is shifted upfield which is in an agreement with the observation made on methylcyclohexanes.[24,25] The carbon-13 resonances of the C-2 methyl carbon of C-2 branched-chain sugars **9–11** are shifted upfield by ~4 ppm (branched-chain sugar **10**) and by ~10 ppm (branched-chain sugars **9** and **11**), with respect to the corresponding C-4 branched-chain sugars (**1–3** and **4–6** and **8**). This upfield shift can be accounted for by the absence of an electronegative substituent, *i.e.*, hydroxyl group, at the C-2 carbon (*e.g.*, carbon-13 resonances of the methyl group in *cis*- and *trans*-4-tert-butyl-1-methylcyclohexan-1-ol[23,26] are deshielded by 6–8 ppm, with respect to the chemical shift of the methyl group in the corresponding methylcyclohexanes[24] depending upon the orientation of the methyl group). The proposed configurational assignments of the C-2 carbon of branched-chain sugars **9–11**, made on the basis of previous findings[23–26] that an equatorially oriented methyl group is deshielded with respect to an axially oriented methyl group, is strongly supported by the chemical shift difference of the C-2 carbon of **9** *vs.* **10** and **11** (*vide supra*) and by the pmr spectra of branched-chain sugars **9–11**. The C-2 hydrogen of **9** appears in the pmr spectrum as a broad multiplet, centered at *ca.* δ 1.8, whereas broad multiplets corresponding to the C-2 hydrogen of branched-chain sugars **10** and **11** are centered at δ 2.4 ppm. The upfield shift (0.6 ppm) of the C-2 hydrogen in **9** with respect to chemical shifts of C-2 hydrogens in **10** and **11** indicates the axial orientation of the C-2 hydrogen and, hence, the equatorial orientation of the C-2 methyl group in **9**. The chemical shift difference between the axially and equatorially oriented methyl group in C-2 epimers **9** and **10** is only 1.4 ppm, instead of being 6 ppm as it was observed for methylcyclohexanes[24,25] and for branched-chain sugars **1–8**.[26] The downfield shift (*ca.* 5 ppm) of the carbon-13 resonance of the axially oriented C-2 methyl group in **10** could be accounted for in the following way. Comparing **9** and **11**, in each instance the C-2 methyl is gauche with respect to the C-1 methoxy group. However, in **11**, the C-2 methyl group

is axially oriented and, therefore, it should exhibit the greater shielding by about 6 ppm (as in 1–8) which is actually observed. By contrast, although the C-2 methyl group of **10** is axially oriented, it should not be as strongly shielded as in **11** because the adjacent C-1 methoxy group is anti to this C-2 methyl group. It is interesting to note the very high field position of the carbon-13 resonance of the axially oriented C-2 methyl group in **11** (5.7 ppm).

Line 5 is assigned to the C-5 carbon. The chemical shift positions of the C-5 carbon of branched-chain sugars **1–8** are approximately the same as the C-5 carbon resonance in methyl α- and β-D-glucopyranosides[30–32] and in β anomers the C-5 carbon is deshielded by a similar amount (4.8 ppm for **3** and **7**, and 4.4 ppm for **6** and **8**). It should be noted that an axial C-4 methyl group shields the C-5 carbon unlike the remainder of the ring carbons (1.7 ppm for **3** and **6**, and 2.1 ppm for **7** and **8**). It has been reported[23] that the carbon-13 resonance of the C-5 carbon of methyl 4,6-*O*-benzylidine-2-deoxy-3-*C*-(1′,3′-dithian-2′-yl)-α-D-*ribo*-hexopyranoside is 59.25 ppm. Using this value, we can calculate, by adding 5 ppm, which is approximately the shielding of the C-5 carbon atom in this branched-chain sugar due to the presence of the axially oriented C-3 hydroxyl group (γ effect), that the carbon-13 resonance of the C-5 carbon atom of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside analog should be ~64.2 ppm, which is in a good agreement with the observed values for chemical shift of the C-5 carbon of branched-chain sugars **9** and **10**, (63.0 and 63.8 ppm). The downfield shift of the carbon-13 resonance of the C-5 carbon of branched-chain sugar **11**, with respect to the C-5 carbon of **10**, can be accounted for by the fact that in the β-anomer the C-5 carbon should be deshielded, in this case by 3.8 ppm.

Taking into account the previous finding[32] that the chemical shifts of the C-3 carbon of methyl α- and β-D-gluco- and -mannopyranosides are 74.8, 76.8, 70.1, and 73.3 ppm and that the methylation of a hydroxyl group causes a downfield shift of 8–11 ppm,[31,33] the chemical shifts given in line 3 must then be assigned to the carbon-13 resonances of the C-3 carbon of branched-chain sugars **1–11**. Furthermore, in β anomers the C-3 carbon is deshielded with respect to the corresponding α anomers by 3.8 ppm (**7** *vs.* **3**), 3.3 ppm (**8** *vs.* **6**), and 2.9 ppm (**11** *vs.* **10**).

Line 4 is assigned to the C-4 carbon. It is the remaining unassigned peak (singlet carbon for branched-chain sugars **1–8**), and the chemical shift position is not significantly different for α and β anomers. The carbon-13 resonances of the C-4 carbon of branched-chain sugars **9–11** are in a good agreement with the reported values for a similar glycopyranoside derivative.[22,23]

Experimental Section

The carbon-13 nmr spectra of branched-chain sugars **3**, **5**, **7**, and **8** were recorded in a $CDCl_3$ solution on a Bruker HFX-90 nmr spectrometer at 22.63 MHz, using a Nicolet FT-1083 computer, by the Fourier transform method. An 8K data table was used for data accumulation yielding 4K transformed spectra on the 5000-Hz sweep width. The spectrometer operates on a fluorine lock and a small amount of C_6F_6 was added to the sample solution for a lock. TMS was used as the internal reference.

The proton noise decoupled carbon-13 nmr spectra of branched-chain sugars **4–6** were recorded in a $CDCl_3$ solution with a Jeol TNM PS-100 FT spectrometer. The spectra were obtained using 5000-Hz sweep width 8K data points.

The carbon-13 nmr spectra of branched-chain sugars **1**, **2**, and **9–11** were recorded in a $CDCl_3$ solution on a Varian CFT-20 carbon-13 nmr spectrometer. The spectrometer operates on a deuterium lock. The spectra were obtained using 4000-Hz sweep width 8K data points.

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Registry No.—**1**, 51016-12-7; **2**, 51016-16-1; **3**, 51016-14-9; **4**, 51016-13-8; **5**, 51016-17-2; **6**, 51016-15-0; **7**, 51016-22-9; **8**, 51016-23-0; **9**, 53011-00-0; **10**, 53011-01-1; **11**, 53011-02-2.

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Application of the Nitrosoamide Reaction to Hydrazones

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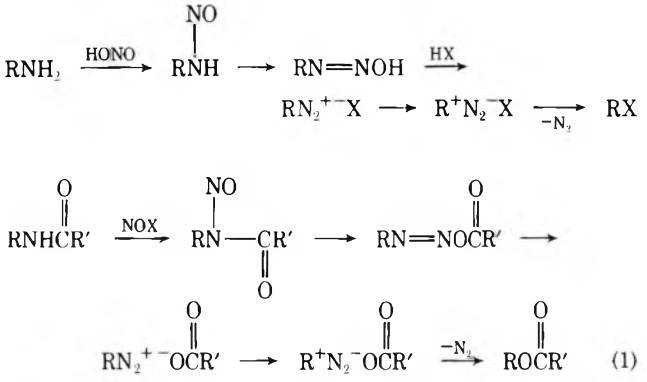
Nitrosation of the *N*-acetylhydrazones of benzophenone, acetophenone, cyclohexanone, and heptaldehyde affords the corresponding 1-acetoxy-1-azido compounds, ketones (or aldehydes), and acetyl azide as the principal products. The unstable *N*-nitrosoamide is undoubtedly formed in the first step of the reaction; a rearrangement to a diazo ester and migration of the carboxylate group complete the process. Minor products of the reaction appear to stem from nitrosation at the imine nitrogen.

The nitrous acid and the nitrosoamide methods for the deamination of aliphatic amines proceed *via* similar intermediates (eq 1).[1] Reports that the reaction of nitrous acid



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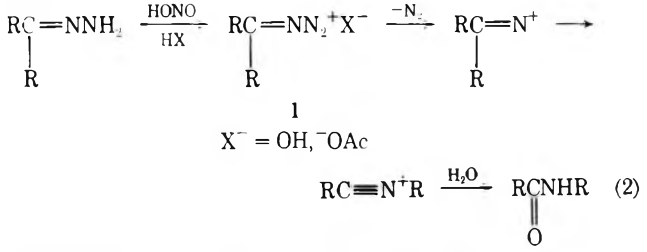
with hydrazones gave a Beckmann type rearrangement (eq 2)[2] suggested to us that the nitrosoamide method of deami-



(2)

nation could be applied to the reaction with advantage, in view of the greater choice of counterion and solvent available with this method. We now report that nitrosation of *N*-acetylhydrazones does not lead to a Beckmann type rearrangement *via* loss of nitrogen from an intermediate iminodiazonium ion such as **1** (X = $^-$OAc); instead, ion recombination occurs to give 1-acetoxy-1-azidoalkanes.

Results and Discussion

N-Acetylhydrazones **2** were prepared by reaction of an aldehyde or ketone with acetylhydrazine. These hydrazones were nitrosated with nitrosyl chloride or dinitrogen tetroxide at −5° in the presence of solid sodium acetate (Chart I). The principal products were identified as the 1-acetoxy-1-azidoalkanes **6**[3] and the corresponding ketone or aldehyde; in some instances, acetyl azide was also detected. The yields of these products are given in Table I.

The presence of the acetoxy azides was easily established from their characteristic ir spectra: a strong azide absorption at ~2120 cm^{-1} and a strong carbonyl absorption at 1750–1780 cm^{-1}. That the ketone or aldehyde and acetyl azide were also present was established by comparison of the ir and nmr spectra with those of the authentic compounds.

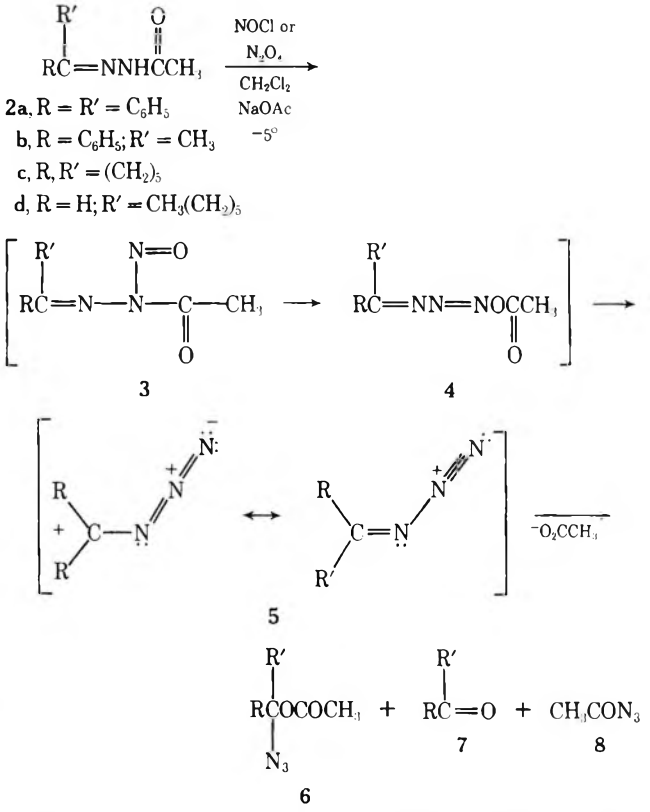
The structure of the acetoxy azides follows from the method of preparation, the physical data (Experimental Section), and the reactions. Attempts to prepare **6a** from benzophenone, acetyl chloride, and sodium azide (or from acetyl azide) were unsuccessful, leading only to the decomposition of the acetyl azide.

Table I
Products from Nitrosation of Hydrazones 2[a]

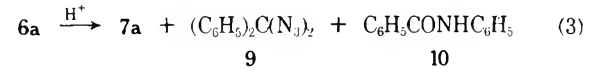
Hydrazone	Products, % Acetoxy azide **6**	Aldehyde or ketone **7**	Acetyl azide **8**
2a	70–86	5–13	
2b	33–63[b]	2–6	
2c	45	35	9–11
2d	20	23	14

[a] Yields were determined by nmr using ethylene bromide as an internal standard. [b] Based on the final product α-azidostyrene.

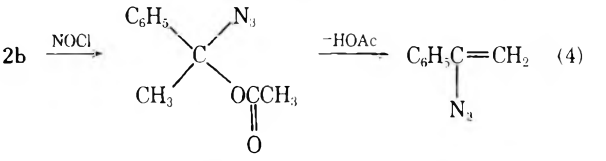
Chart I



The acetoxy azides **6** were further characterized by their reactions. Chromatography of azide **6a** on silica gel led to decomposition; diazidodiphenylmethane[4] (39%), benzophenone (56%), and benzanilide (9%) were formed (eq 3). Treatment of **6a** with gaseous hydrogen chloride led to formation of benzophenone (65%) and benzanilide (15%). Prolonged treatment of **6a** with aqueous sodium carbonate caused a slow conversion to benzophenone.

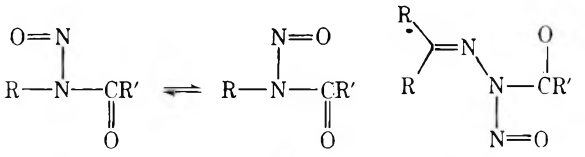


Nitrosation of hydrazone **2b** gave the acetoxy azide **6b** as a short-lived intermediate. An nmr spectrum of the reaction mixture showed methyl singlets at δ 1.91 and 2.11 that are assigned to **6b**; the ir spectrum showed a strong azide absorption at 2120 cm^{-1} and a carbonyl band at 1760 cm^{-1}. In addition, the nmr spectrum indicated that a small amount (5–10%) of another product, α-azidostyrene, was also present by the appearance of olefinic protons at δ 4.91 (d, J = 2 Hz) and 5.37 (d, J = 2 Hz). Furthermore, on standing for 24 hr, the signals assigned to **6b** were observed to decrease in size accompanied by a proportional increase in the area of the peaks belonging to the α-azidostyrene. Thus, acetoxy azide **2b** slowly eliminates acetic acid to give α-azidostyrene (eq 4), presumably *via* an E1-type pathway.



The azides **6c** and **6d** showed no tendency to decompose to vinyl azides. An attempt was made to promote elimination of acetic acid from azide **6c** by using the "proton sponge" bis-1,8-(dimethylamino)naphthalene;[5] no reaction occurred during 24 hr.

By analogy with the nitrosation of amides and carbamates,[1] we propose that in the first step of the reaction (Chart I) nitrosation occurs to give the unstable *N*-nitroso-*N*-acetylhydrazone **3** followed by rapid rearrangement to a diazo ester **4** and dissociation to the ion pair **5**. Efforts to detect **3** in the reaction mixture were unsuccessful. An ir spectrum run immediately after the addition of nitrosyl chloride showed only acetoxy azide **6** and unreacted hydrazone. The stability of *N*-nitrosoamides and related compounds is a sensitive function of the size of the alkyl group (R in **11**); large groups favor conformer **b** in which the ni-

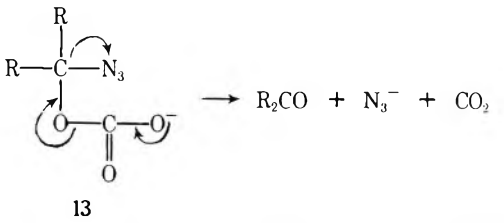


troso group is favorably positioned for attack on the carbonyl group (Chart I).[6] In the nitrosoacylhydrazones, the reactive system is undoubtedly planar and nonbonded interactions of the nitroso function with the R groups should favor the reactive conformer shown in **12**, leading to instability of the compounds.

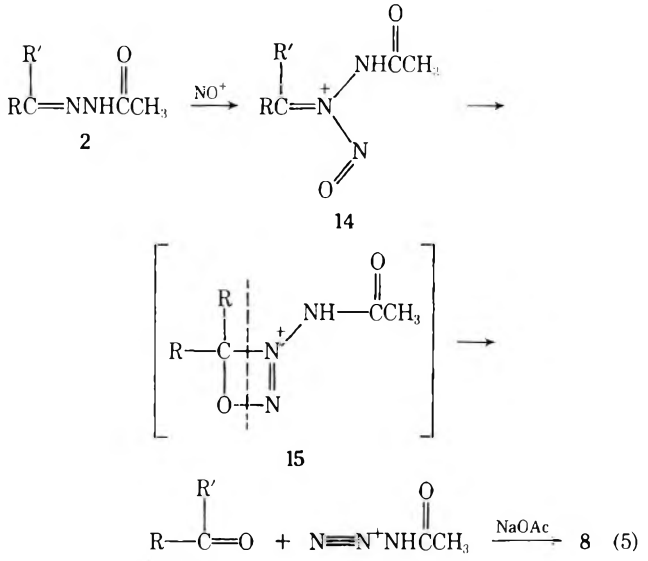
External anions are known to participate in the nitrosoamide reaction.[1] Similarly, when sodium propionate was substituted for the sodium acetate in the nitrosation of **2a**, 1-propionoxy-1-azidodiphenylmethane (14%) was detected as one of the products together with the corresponding acetate **6a** (82%). A control experiment showed that the acetate group of **6a** does not exchange with sodium propionate under the reaction conditions. Thus, the exchange occurs with **4** or more probably with **5**.

A second example of the involvement of anions from the medium was found in the nitrosation of **2b** in the presence of sodium carbonate.[7] Only acetophenone was formed, presumably *via* **13**. Similar reactions of nucleophiles with the acetoxy azides **6** can account for the excess of carbonyl compounds formed over acetyl azide (Table I).

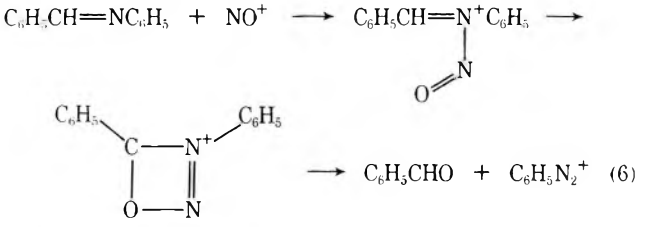
The formation of acetyl azide cannot be readily ex-



plained by the mechanism outlined in Chart I. This compound probably stems from the processes outlined in eq 5.



Since the basicities of the two nitrogens in the hydrazones **2** are comparable,[8] nitrosation should be capable of occurring at either site. It appears reasonable that the *N*-nitrosoimine **14** could decompose to a ketone and acetyl azide through the oxadiazetine intermediate **15**. Doyle, *et al.*,[9] and others[10] have proposed analogous four-membered intermediates to account, for example, for the formation of benzaldehyde and benzenediazonium ion from nitrosation of *N*-benzylideneaniline (eq 6).[11a,b]

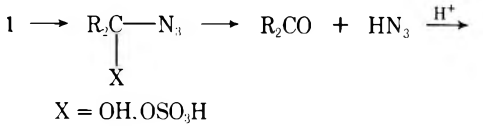


In an effort to avoid the processes outlined in eq 5 and favor nitrosation of the amide nitrogen, the sodium salt of hydrazone **2c** was prepared and treated with nitrosyl chloride in the usual manner. The yield of acetoxy azide **6c** was greater than in the normal procedure (62% *vs.* 45%) and acetyl azide was not detected. Acetyl azide was never detected in the nitrosation of **2a** or **2b** implying that the phenyl groups make the imine nitrogen less susceptible to nitrosation compared with the amide nitrogen, probably due to an electron withdrawal effect.

Relationship to the Beckmann and Schmidt Reactions. The reactions described above show that if the counterion in species **1** is a strong base such as acetate ion, elimination of nitrogen does not compete with ion recombination to form species **6**. That is, in the nitrosation of compound **2a**, **6a** was formed, not benzanilide, of which only a trace was detected.

In the deamination analogy to the Beckmann reaction (eq 2),[2] 90% sulfuric acid was used as the medium, and it is possible that the availability of only bisulfate ion or water (low concentration) as nucleophiles conferred a sufficient

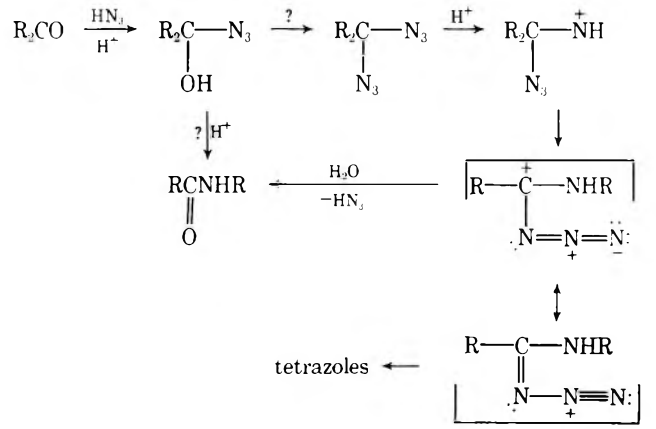
lifetime to species **1** to allow nitrogen elimination to occur (eq 2). However, it is also possible that the reaction really proceeds *via* eq 7. In any case, the first two steps of eq 7 al-



"Schmidt-type reactions" (7)

most certainly occur in dilute acid solutions in view of the high yields of carbonyl compounds formed under those conditions.[8b]

The conversion of **6a** to **9** under acidic conditions suggests the possibility, furthermore, that diazidoalkanes may be involved as intermediates in the Schmidt reaction.



(8)

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 457A spectrometer and ultraviolet spectra on a Cary Model 14 spectrophotometer. The nmr spectra were recorded with Varian Model A-60 and HA-100 instruments.

Acetylhydrazones (2a–d). Following the procedure of Grammaticakis,[12] equimolar amounts of the ketone or aldehyde and acetylhydrazine[13] were mixed. The reaction mixture became warm and homogeneous followed by formation of a solid mass. After 18–24 hr, the solid product was recrystallized to afford white crystals (40–80%). For benzophenone, the ketone and acetylhydrazine (2 molar excess) were dissolved separately in absolute methanol and then mixed. A drop of sulfuric acid was added and the reaction solution was refluxed for 6 hr. Water and ether were then added, and the ether layer was separated, dried over $MgSO_4$, and concentrated to give a white solid. A small amount of unreacted benzophenone was removed by recrystallization from methanol.

Benzophenone-*N*-acetylhydrazone (2a): mp 105–106° (lit.[14] 107°); ir (CCl_4) 3335 (w, NH), 1710 (s), 1680 (m), 1450 (m), 1370 cm^{-1} (m); nmr ($CDCl_3$) δ 2.42 (s, 3 H), 7.1–7.7 (m, 10 H), 8.4 (s, NH).

Acetophenone-*N*-acetylhydrazone (2b) (recrystallized from methanol): mp 128–131° (lit.[15] 131–132°); ir (CCl_4) 3200 (w), 3100 (w), 1670 (s), 1395 (m), 1345 cm^{-1} (m); nmr (CCl_4) δ 2.33 (s, 6 H), 7.2–7.4 (m, 3 H), 7.6–7.9 (m, 2 H), 10.7 (s, NH).

Cyclohexanone-*N*-acetylhydrazone (2c) (recrystallized from methanol–ether): mp 123–124°; ir (CCl_4) 3195 (w), 3095 (w), 1670 (s), 1395 cm^{-1} (m); nmr (CCl_4) δ 1.5–1.9 (br m, 6 H), 2.18 (s, 3 H), 2.1–2.65 (m, 4 H), 10.3 (s, NH).

Heptaldehyde-*N*-acetylhydrazone (2d) (recrystallized from ether): mp 40–45°; ir (CCl_4) 3190 (w), 3090 (w), 1670 (s), 1400 (m), 1340 cm^{-1} (m); nmr (CCl_4) δ 0.90 (t, 3 H), 1.1–1.8 (m, 8 H), 2.15 (s, 3 H), 2.0–2.4 (m, 2 H), 7.25 (t, 1 H), 10.8 (s, NH).

Nitrosation of Benzophenone-*N*-acetylhydrazone. (A) With Dinitrogen Tetroxide. In a 50-ml flask was placed 0.61 g (2.56 mmol) of hydrazone **2a**, 3 g (37 mmol) of anhydrous sodium acetate, and 10 ml of dichloromethane. The reaction vessel was equipped with a drying tube and cooled in a Dry Ice–acetone bath. Dinitrogen tetroxide (0.5 ml, 0.7 g, 8.1 mmol) was added as a liquid in one portion, and the Dry Ice–acetone bath was replaced with an ice bath. After 2.5 hr of stirring, the mixture was filtered and evacuated under vacuum (25°, 20 μ) to remove acetic acid. The product was an oily residue, largely the acetoxy azide **6a**: ir (CH_2Cl_2) 2120 (s), 1760 (s), 1495 (m), 1450 (m), 1370 (m), 1220 (s), 1190 (m), 1185 (m), 1000 cm^{-1} (m); nmr ($CDCl_3$) δ 2.2 (s, 3 H), 7.0–7.9 (m, 10 H); mass spectrum *m/e* (rel intensity) 239 (4, P − 28), 197 (54), 194 (19), 182 (100), 105 (100). The yield was 70% as determined by nmr using ethylene dibromide as an internal standard. The presence of benzophenone was indicated by a weak carbonyl band at 1660 cm^{-1} in the ir spectrum; the absolute yield was estimated to be about 10% from the nmr integration.

Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.42; H, 4.87; N, 15.73. Found; C, 68.04; H, 5.08; N, 15.08.

This analysis is correct if 3–4% benzophenone is present. Ir and nmr spectra indicate this is probably so. Attempts to further purify the sample led to decomposition of **6a**.

Refluxing the crude product in carbon tetrachloride for 24 hr or hexane for 72 hr caused no apparent change in **6a**. Treatment of **6a** dissolved in carbon tetrachloride with aqueous sodium carbonate (saturated) caused a 15% increase in benzophenone within 4 hr at room temperature.

The oily azido compound **6a** (3.5 g) was chromatographed on silica gel (50 g) and fractions of 125 ml were taken. Five fractions of 100% petroleum ether, then two each of 2.5, 5.0, 7.5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90% ether in petroleum ether, and finally five fractions of 100% ether were collected. Fractions 2 and 3 contained 1.27 g (5.1 mmol, 39%) of a white, crystalline solid that was recrystallized from pentane and identified as diazidodiphenylmethane: mp 40.5–41.0° (lit.[4a] 42°); ir (CCl_4) 3320 (w), 3060 (w), 2440 (w), 2120 (s), 2005 (s), 1220 cm^{-1} (s); mass spectrum *m/e* (rel intensity) 194 (51), 119 (39), 103 (100), 93 (39), 91 (26), 77 (21), 76 (34); uv (hexane) 259 nm (ϵ 620).

Anal. Calcd for $C_{13}H_{10}N_6$: C, 62.40; H, 4.00; N, 33.60. Found: C, 62.22; H, 4.03; N, 34.14.

Pyrolysis of the diazide and recrystallization of the product from chloroform yielded a crystalline solid which was identified as 1,5-diphenyltetrazole: mp 143–145° (lit.[4b] 146°).

Fractions 7–10 gave 1.34 g (7.4 mmol, 56%) of a viscous liquid that was identified as benzophenone by ir comparison. Fractions 14–17 contained a solid that was identified as benzanilide (0.24 g, 1.2 mmol, 9%) by comparison of the ir spectrum with authentic material. Recrystallization from carbon tetrachloride yielded white crystals melting at 161–162° (lit.[16] 163°).

Similar yields of benzophenone (65%) and benzanilide (15%) were obtained when the azide **6a** was treated with gaseous hydrogen chloride in ether at 25° for 3 days.

(B) With Nitrosyl Chloride. In a flask fitted with a drying tube and serum cap was placed 0.28 g (1.18 mmol) of hydrazone **2a**, 1.6 g (20 mmol) of anhydrous sodium acetate, and 6 ml of dichloromethane. The reaction vessel was cooled in an ice–acetone bath (~−5°) and 26 ml (78 mg, 1.2 mmol) of gaseous nitrosyl chloride was injected from a syringe into the rapidly stirred mixture. After 30 min at 0°, an ir spectrum of the reaction mixture showed the presence of unreacted **2a** plus new bands at 2120 (s), 1760 (s), 1715 (s), 1295 (s), and 1220 cm^{-1} (s). An additional 48 ml of nitrosyl chloride was added in three portions until the hydrazone could not be detected by ir. The reaction mixture was filtered; the filtrate was concentrated on a rotary evaporator and evacuated further (30 μ) to remove most of the acetic acid. An ir spectrum of the oily residue was identical with **6a** as prepared using dinitrogen tetroxide. The yield of **6a** was calculated to be 78% by nmr. Benzophenone (5%) was also present. Similar results were obtained in other runs when the nitrosyl chloride was added in one batch.

(C) In the Presence of Sodium Propionate. To a mixture of 0.193 g (0.81 mmol) of **2a** and 1.5 g (14 mmol) of sodium propionate in 6 ml of dichloromethane was added 50 ml (2.3 mmol) of gaseous nitrosyl chloride. After 25 min, the reaction mixture was filtered. The filtrate was washed sequentially with water and a saturated solution of sodium carbonate; it was then dried over sodium sulfate and concentrated on a rotary evaporator. The residue was dissolved in carbon tetrachloride and a weighed amount of ethylene bromide was added as an internal standard. The nmr spectrum showed that **6a** (82%) was present and also 1-azido-1-propionoxydiphenylmethane (14%): nmr (CCl_4) δ 1.1 (t, 3 H), 2.3 (q, 2 H), 7.2–7.5 (m, 10 H). Benzophenone (3%) was also present.

For a control, a mixture of 188 mg (0.70 mmol) of **6a**, 1.5 g (14 mmol) of sodium propionate, 85 mg (1.14 mmol) of propionic acid, and 25 ml of nitrosyl chloride was stirred for 25 min at 0°, filtered, and worked up exactly as described above. The nmr spectrum of the product showed **6a** was recovered unchanged. No signals in the

nmr spectrum were detected that could be attributed to a propionate group (<1%).

(D) With Pyridine. To a mixture of 0.55 g (2.3 mmol) of **2a,** 0.2 ml (2.5 mmol) of pyridine, and 10 ml of dichloromethane was added 55 ml (2.3 mmol) of gaseous nitrosyl chloride. An ir spectrum showed that **6a** had formed, but some unreacted **2a** still remained. Addition of more nitrosyl chloride (25 ml) caused decomposition of **6a** to benzophenone and diazidodiphenylmethane as determined by the ir spectrum.

Nitrosation of Acetophenone-*N*-acetylhydrazone. (A) A mixture of 300 mg (1.8 mmol) of hydrazone **2b** and 1.9 g (23 mmol) of sodium acetate in 8 ml of dichloromethane was allowed to react with 30 ml (1.3 mmol) of gaseous nitrosyl chloride in the same manner as previously described for **2a.** After 30 min an ir spectrum of the reaction mixture showed the presence of unreacted **2b** in addition to new bands at 2120 (s), 1760 (s), 1715 (s), and 1220 cm^{-1} (m). An additional 30 ml of nitrosyl chloride was added and after stirring the reaction mixture for 30 min more, it was filtered. The nmr spectrum of the filtrate showed methyl singlets at δ 1.90 and 2.1 that are assigned to the acetoxy azide **6b,** at δ 2.04 (acetic acid), δ 2.24 and 2.34 (unreacted **3b**), and δ 2.54 (acetophenone). After standing for 24 hr at room temperature in dichloromethane, the singlets at δ 1.90 and 2.1 decreased in size by 67% with a corresponding increase in the acetic acid peak. After 2 days, ir and nmr spectra showed that compound **6b** had completely disappeared. The filtrate was washed with a saturated solution of sodium carbonate, dried, and concentrated on a rotary evaporator. The nmr and ir spectra of the residue indicated that α-azidostyrene (0.60 mmol, 33%), acetophenone (0.04 mmol, 2%), and unreacted **2b** (0.2 mmol, 11%) were present. The α-azidostyrene was identified by the following data which agreed with the nmr and ir values reported in the literature:[17] nmr (CCl_4) δ 4.91 (d, J = 2.0 Hz, 1 H), 5.37 (d, J = 2.0 Hz, 1 H), 7.2–7.8 (m, 5 H); ir (CCl_4) 2220 (w), 2140 (s), 2105 (s), 1615 (m), 1300 (s), and 840 cm^{-1} (m).

In a duplicate run, 0.76 g (4.3 mmol) of **2b,** 5.0 g of sodium acetate, 19 ml of dichloromethane, and 200 ml of nitrosyl chloride were treated in the same manner. After 2 days at room temperature, the reaction mixture was worked up as before. The volatiles were collected and analyzed by ir for acetyl azide; none was detected (<1%). The residue was dissolved in CCl_4 and ethylene bromide was added as an internal standard. The nmr spectrum showed that α-azidostyrene (2.7 mmol, 63%), acetophenone (0.2 mmol, 5%), unreacted hydrazone **2b** (0.8 mmol, 19%), and some **6b** (0.26 mmol, 6%) were present.

(B) With Sodium Carbonate. Nitrosation was carried out in 50 ml of dichloromethane with 1.76 g (10.0 mmol) of **2b,** 5.3 g (50 mmol) of sodium carbonate, and 480 ml (20 mmol) of nitrosyl chloride as described above. The nitrosyl chloride was added over 20 min, and after an additional 20 min, the reaction mixture was filtered and evaporated at 0.01 Torr. The nmr spectrum of the resulting oil showed acetophenone (δ 2.5), acetic acid (δ 2.0), and unidentified peaks (δ 1.9–2.3) in a relative ratio of 16:1:3. The total product was distilled under reduced pressure (20 mm) to give 0.86 g (7.2 mmol, 72%) of acetophenone.

Nitrosation of Cyclohexanone-*N*-acetylhydrazone. A mixture of 0.58 g (3.75 mmol) of hydrazone **2c** and 4.0 g of anhydrous sodium acetate in 16 ml of dichloromethane was allowed to react with 30 ml (1.38 mmol) of gaseous nitrosyl chloride in the usual manner. The ir spectrum of the mixture showed an azide absorption at 2125 cm^{-1} (m), a strong carbonyl band at 1715 cm^{-1} (unreacted **2c**), and weak bands at 1745, 1220, and 1200 cm^{-1}. An additional 120 ml of nitrosyl chloride was added in two portions to bring the total to 150 ml (5.9 mmol). The reaction mixture was stirred another 20 min, then filtered and washed with a saturated solution of sodium carbonate. An ir spectrum of the resulting solution showed the following strong absorptions: 2125, 1745, 1715, 1375, 1220, and 1200 cm^{-1}. The solvent was removed under vacuum (20 mm) and the volatiles were trapped. The ir spectrum of the volatiles showed the presence of acetyl azide: 2135 (s), 1715 (s), 1370 (m), 1200 (s), 1150 (w), 990 cm^{-1} (m). This spectrum was identical with a spectrum of acetyl azide prepared from acetyl chloride and sodium azide in dichloromethane.[18] The nmr spectrum of the volatiles showed a singlet for acetyl azide at δ 2.0, and the yield was calculated to be 9% by using ethylene bromide as an internal standard. The yield was 11% on a duplicate run.

After removal of the volatiles, the ir spectrum (CH_2Cl_2) of the residue showed bands at 2125 (s), 1750 (s), 1710 (s), 1370 (m), and 1220 cm^{-1} (m). These bands are consistent with the presence of **6c** and cyclohexanone. The yields were estimated by nmr to be 45 and 35%, respectively.

Nitrosation of the Sodium Salt of Hydrazone 2c with Nitrosyl Chloride. A three-necked 100-ml flask was fitted with a nitrogen inlet, condenser with a drying tube, stirring bar, and serum cap. Dry toluene (25 ml) and 0.51 g (3.3 mmol) of compound **2c** were added, and the mixture was heated in an oil bath. At 50–60°, the mixture became homogeneous, and 91 mg (3.95 mmol) of sodium was added. Hydrogen evolution was moderate. The reaction mixture was heated at 100–110° for 4 hr during which time the sodium slowly disappeared and a copious white precipitate formed. The reaction mixture was cooled, and the toluene was removed under vacuum (0.1 mm). To the white residue was added 20 ml of dichloromethane and 2.0 g (22 mmol) of sodium acetate. The mixture was cooled in an ice–acetone bath and 30 ml of gaseous nitrosyl chloride was injected *via* a syringe. This action was repeated over a 1-hr period until a total of 150 ml (6.9 mmol) of nitrosyl chloride had been added. The reaction mixture was filtered. An ir spectrum of the filtrate revealed the presence of the acetoxyazido compound **6c** and some cyclohexanone, but no acetyl azide (<5%). The ir spectrum of the filtrate showed no change after 24 hr or after shaking with an aqueous solution saturated with sodium carbonate. The solvent was removed on a rotary evaporator to give 0.41 g of a liquid. A portion (180 mg) was chromatographed over Florisil eluting with a 5% dichloromethane–hexane solution. The first three fractions contained a single component (60 mg) identified as the acetoxyazido compound **6c** on the following basis: ir (CCl_4) 2940 (s), 2860 (m), 2110 (s), 1750 (s), 1365 (m), 1265 (s), 1220 cm^{-1} (s); nmr (CCl_4, 100 MHz) δ 1.41–1.76 (m, 6 H), 1.86–2.06 (m, 2 H), 2.01 (s, 3 H), 2.12–2.41 (m, 2 H); mass spectrum *m/e* (rel intensity) 155 (26), 127 (27), 113 (40), 112 (27), 98 (22), 85 (92), 60 (100). The yield in the crude product mixture was estimated to be 62% by nmr using an internal standard (ethylene bromide). A small amount of cyclohexanone was also present (~10–20%) as indicated by a weak carbonyl absorption at 1715 cm^{-1}.

Nitrosation of Heptaldehyde-*N*-acetylhydrazone. A mixture of 0.61 g (3.6 mmol) of hydrazone **2d** and 4.0 g (44 mmol) of sodium acetate in 15 ml of dichloromethane was nitrosated with 200 ml (9.2 mmol) of nitrosyl chloride in the usual manner. An ir spectrum taken after adding 50 ml of nitrosyl chloride showed new absorptions at 2135, 1200 (acetyl azide), and 1715 cm^{-1}. After adding the remainder of the nitrosyl chloride, the reaction mixture was filtered. An ir spectrum of the filtrate showed large amounts of acetic acid in addition to acetyl azide. The filtrate was then washed with a saturated solution of sodium carbonate. An ir spectrum (CH_2Cl_2) showed that a second azide product (**6d**) was present together with heptaldehyde and acetyl azide. The solvent was removed under vacuum and the volatiles were collected. The ir spectrum of the volatiles showed that acetyl azide was present; the yield by nmr was 14%. The residue showed the presence of the acetoxy azide **6d** [ir (CH_2Cl_2) 2120 (s), 1760 (s), 1210 cm^{-1} (s); nmr (CCl_4) δ 2.05 (s, 3 H), 5.78 (t, 1 H)] and heptaldehyde [ir (CH_2Cl_2) 2720 (w), 1730 cm^{-1} (s); nmr (CCl_4) δ 9.65 (t, 1 H)]. The yields were 23% for aldehyde and 20% for **6d** as determined by nmr on the crude product using ethylene bromide as an internal standard.

The acetoxy azide **6d** remained unchanged at room temperature over a period of a week or when it was heated in refluxing carbon tetrachloride for several hours. The mixture of products was chromatographed over silica gel eluting with carbon tetrachloride. Decomposition of **6d** was not observed, but there was little separation of **6d** and heptaldehyde.

Attempted Preparation of 1-Azidocyclohexene. To a solution of 28 mg of acetoxy azide **6c** in CCl_4 was added 65 mg of 1,8-bis(dimethylamino)naphthalene. The nmr spectrum was recorded several times over a 24-hr period. There was no change in **6c.**

Acknowledgment. We thank the National Science Foundation for its support of this work (GP-8993).

Registry No.—**2a,** 52919-86-5; **2b,** 28153-25-5; **2c,** 28766-50-9; **2c** Na salt, 52919-88-7; **2d,** 52919-87-6; **6a,** 52919-89-8; **6b,** 52919-90-1; **6c,** 52919-91-2; **6d,** 52919-92-3; **7a,** 119-61-9; **7b,** 98-86-2; **7c,** 108-94-1; **7d,** 111-71-7; acetylhydrazine, 1068-57-1; dinitrogen tetroxide, 10544-72-6; nitrosyl chloride, 2696-92-6; diazidodiphenylmethane, 17421-82-8; 1-azido-1-propionoxydiphenylmethane, 52964-38-2.

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Peracid Oxidation of Imino Ethers[1]

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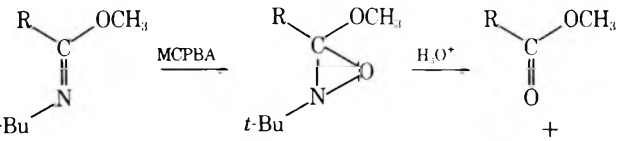
Peracid oxidation of imino ethers results in the formation of 3-alkoxyoxaziranes. The oxidation of the 2-alkoxyazetines **15**, **18**, and **22** leads to unstable 1-aza-5-oxabicyclo[2.1.0]pentanes and Baeyer–Villiger products, 2-alkoxy-2-oxazolines. The product distribution depends upon the substitution at the migrating center. These 2-alkoxy-2-oxazoline products represent the first examples of Baeyer–Villiger type oxidation of imines. The oxaziranes **9** and **10** derived from the cyclic imino ethers **7** and **8** can be isolated, but readily rearrange to imino esters **11** and **12** thermally. The hydrolysis of alkoxyoxaziranes yields esters and hydroxylamines, but hydrolysis of the bicyclic oxaziranes **9** and **10** leads to cyclic hydroxamic acids as well. Further oxidation of alkoxyoxaziranes gives esters and nitroso compounds. The nitroso compounds dimerize if tertiary or tautomerize to oximes if secondary. Oxidation of 2-alkoxyoxazoline **19** (an imino carbonate) results in the formation of a nitroso carbonate **29**, by a double oxidation sequence. Oxidation of imino ethers with 2 equiv of peracid provides a convenient synthetic method for cleavage of the C=N bond.

The oxazirane ring system was first synthesized in 1956 by peracid oxidation of imines.[3-8] Since then, many oxaziranes have been prepared by this method as well as new ones.[9-30] The ring strain and electronegative elements of the oxazirane ring make it unique in its physical and chemical properties. Oxaziranes, for example, have an unusually high barrier to nitrogen inversion (ref 4, 16, 17, 26, 27, 31, 32). Thermally, oxaziranes rearrange to nitrones (ref 3, 4, 6, 8, 11, 15, 26–28) (as low as −8°),[12] amides (generally above 150°) (ref 4, 9, 10b, 26–28, 30), or a carbonyl compound plus an imine (ref 4, 12, 13, 26, 27). Photochemically, oxaziranes open to give nitroxides,[28,33a] nitrenes,[28] or amides.[28,33b,c] Hydrolytically, oxaziranes can decompose to carbonyl compounds, hydroxylamines, and ammonia or imines, the products dependent upon the pH and the substituents of the oxazirane (ref 3, 4, 6, 9, 10b, 26, 27, 30, 34a,b, 35a,b). Some interesting cycloaddition reactions with heterocumulenes have recently been investigated by Agawa and coworkers.[36,37]

While many imines have been oxidized to oxaziranes, no imino ethers have been oxidized before.[1,22] Imino ethers are readily available by alkylation of amides and lactams[38-41] and other methods.[42] Of particular interest are the alkoxyazetines derived from alkylation[43,44a,b] of β-lactams available from addition of chlorosulfonyl isocyanate to olefins.[45,46] This constitutes nearly the only entry into the azetine ring system.[47] We describe here the oxidation of some cyclic and acyclic imino ethers and some properties of the derived alkoxyoxaziranes.

Results and Discussion

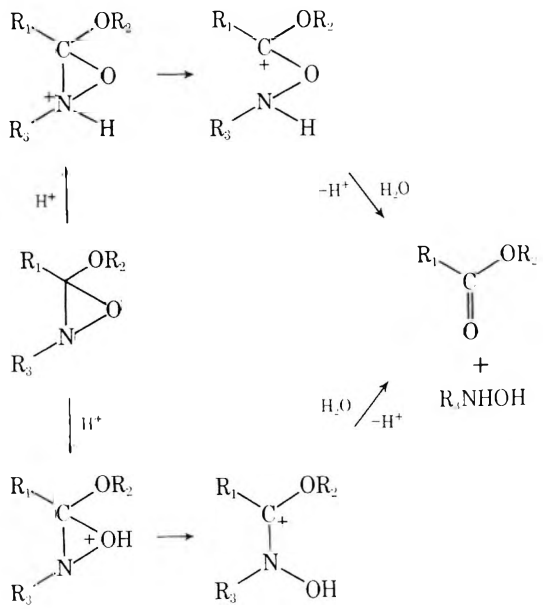
Oxidation of Acyclic Imino Ethers. Oxidation of imino ethers **1** and **2** using *m*-chloroperbenzoic acid (MCPBA) gives the oxaziranes **4** and **5** in good yields. Oxazirane **4** is stable to aqueous base, but treatment with aqueous acid results in the formation of methyl formate (95% by nmr) and *N-tert*-butylhydroxylamine (87% by nmr). This reaction sequence can be used to synthesize hydroxylamines from the corresponding amides in two steps.[4,27] The acid hydrol-



1, R = H
2, R = *t*-Bu
3, R = CH_3

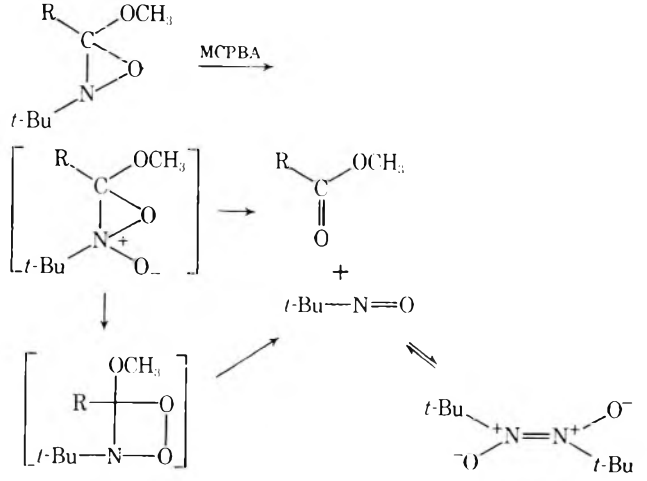
4, R = H
5, R = *t*-Bu
6, R = CH_3

ysis of 3-alkoxyoxaziranes yields products analogous to those obtained from 3-phenyloxaziranes.[3,4,10b,34a,b,35a] Two routes are possible, considering alkoxyoxaziranes as cyclic amide acetals.[48] Protonation on oxygen with C–O bond cleavage has been suggested for this process with most oxaziranes,[4,34a,b,35a] although protonation on nitrogen with C–N bond cleavage is the preferred mode for cleavage of acyclic amide acetals in acid.[48] The C–O cleavage is favored only in neutral hydrolysis of amide acetals.[48] Apparently no N–O cleavage occurs. If it had occurred, a simultaneous

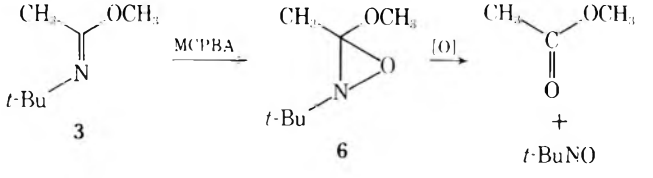


migration from carbon to nitrogen of the 3 substituent would be expected, giving an amine and two carbonyl compounds as observed with some oxaziranes.[4,34a,35a,b] The methoxy substituent probably directs ring cleavage to the ring C–O bond rather than the N–O bond, while ring strain directs cleavage to the ring C–O bond rather than the external C–O bond.

The oxazirane **4** can be oxidized further with MCPBA to give methyl formate (76% by nmr), 2-methyl-2-nitrosopropane (17.5% by nmr) as-a blue liquid, and the solid *trans*-nitroso dimer (58.5% by nmr). The nitroso compounds were independently synthesized by oxidation of *tert*-butylamine using MCPBA.[49] Nitroso compounds have previously been found to result from the peracid oxidation of oxaziranes[4,5,9,14,26,27] and aziridines.[50a] Such reactions were postulated to involve an *N*-oxide which undergoes elimination of the nitrosoalkane,[50b] apparently nonstereospecifically in the case of the aziridine *N*-oxides.[50a] The reaction

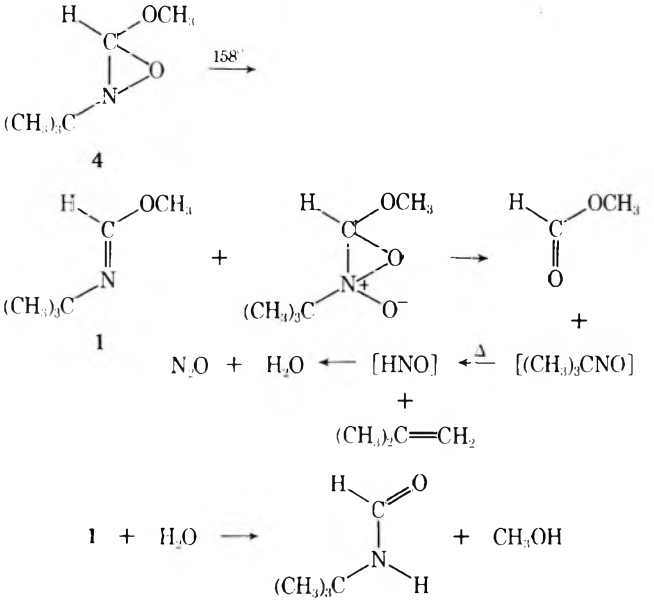


may also go by ring expansion to the unknown dioxazetidine ring system, which would probably cleave readily to the nitrosoalkanes.[51] Curiously, oxidation of the imino ether **3** gives only 5% of the oxazirane **6** along with recovered starting material when a 1:1 ratio of MCPBA and



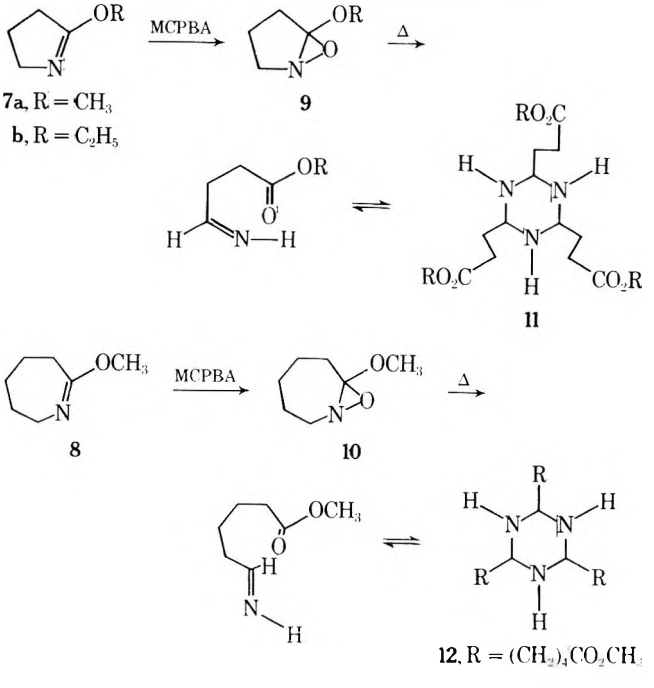
imino ether is used. The oxazirane **6** is especially sensitive to overoxidation and the major products formed are methyl acetate and 2-methyl-2-nitrosopropane.

Oxazirane **4** was subjected to vacuum pyrolysis at 158°. The observed products were isobutene (10%), methyl formate (11%), *N-tert*-butylformamide (7%), imino ether **1** (6%), and methanol (18%). Approximately 4% recovered oxazirane **4** and a nonvolatile residue comprise the remainder of the material. Apparently the primary reaction occurring in this pyrolysis is disproportionation of **4** to **1** and the cyclic *N*-oxide, followed by secondary decomposition and hydrolysis of **1**. Analogous products have been characterized in the thermolysis of 2-*tert*-butyl-3-phenyloxazirane,[4,32]



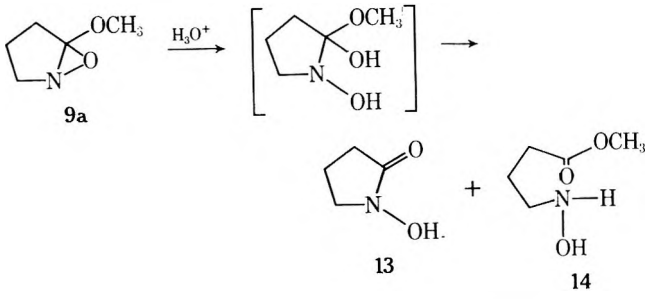
which gives parent imine, benzaldehyde, 2-methyl-2-nitrosopropane, isobutene, and nitrous oxide along with nitrone. Oxaziranes without 3-phenyl substituents normally give amides[4,9,26-28] and oxaziranes with abstractable protons on the 2 substituent normally give a carbonyl compound plus an imine.[4,13,32]

Oxidation of Cyclic Imino Ethers. Oxidation of imino ethers **7** and **8** gives oxaziranes **9** and **10**. In contrast to **4**, oxaziranes **9** and **10** are unstable thermally. The best conditions for formation of **9** and **10** are oxidation in dichloro-



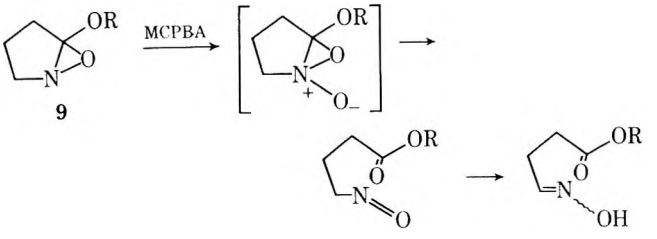
methane[18] at low temperature (−40°) with added solid potassium carbonate. Under these conditions and after careful work-up, yields of **9** are *ca.* 60%. These oxaziranes can decompose violently when concentrated at room temperature. The decomposition of these oxaziranes in dilute solution requires an induction period. Decomposition of oxazirane **9b** results in the formation of ethyl 4-iminobutanoate, isolated as its trimer **11b.** The trimer **11b** was further characterized by conversion to the 2,4-dinitrophenylhydrazone and semicarbazone of ethyl 4-oxobutanoate. The formation of imine esters appears to proceed by a radical chain mechanism analogous to other oxaziranes.[4,26,27] This decomposition for **7** and **8** takes place much more readily and at lower temperatures than for other oxaziranes. The mechanism requires an abstractable hydrogen atom on the carbon next to nitrogen.

Hydrolysis of the above bicyclic oxaziranes was studied using oxazirane **9a.** Treatment of **9a** with aqueous acid results in the formation of methyl 3-hydroxyaminobutanoate (**14**) (17%), *N*-hydroxypyrrolidone (**13**) (27%), and methanol. The hydroxamic acid **13** yields a characteristic dark violet solution upon treatment with ferric chloride solution.[52] Hydrolysis of the oxazirane **10** has been found to yield an analogous hydroxamic acid in 3% yield.[22] Isolated yields of hydroxamic acids are low possibly because of their water solubility. With the isolation of hydroxamic acids from the bicyclic oxaziranes, it is of interest to know if any hydroxamic acids are formed at all from the acyclic oxaziranes upon hydrolysis. Following the same procedure for hydrolysis of oxazirane **9a,** oxazirane **4** gives an essentially quantitative yield of *tert*-butylhydroxylamine with no evidence of hydroxamic acid formation. Testing the reaction mixture with ferric chloride solution was negative for the presence of hydroxamic acids. Hydroxamic acid **13** could be formed from the intermediate shown below along with hydroxylamine **14,** or be the product of cyclization of hydroxylamine

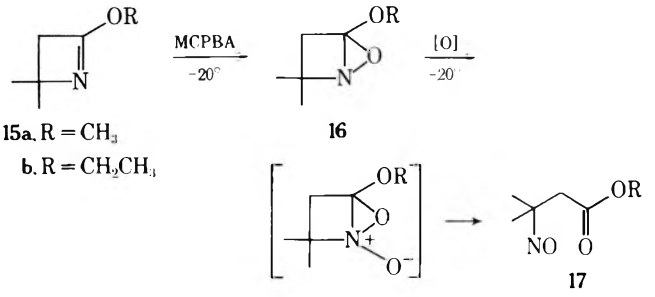


14. Cyclic hydroxamic acids have been obtained by reduction of nitro esters, presumably by cyclization of the hydroxylamino esters.[53,54]

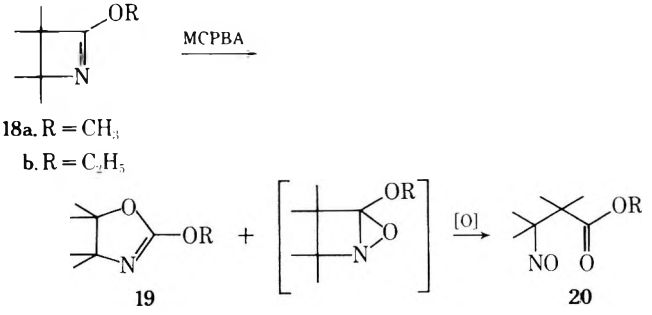
Oxidation of **9** with MCPBA gives methyl alkyl isonitrosobutanoates. Such oxime esters are also isolated as overoxidation products in the preparation of oxaziranes **9** and **10.** These oximes must be derived from tautomerization of the initially formed nitroso compounds. Oxidation of **8** also gives some methyl 5-cyanopentanoate,[22] perhaps by dehydration of the oxime.



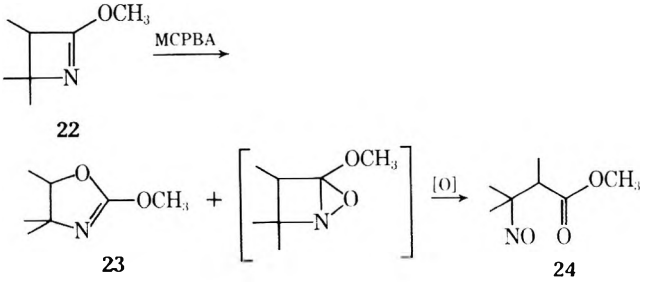
Because of the radical induced rearrangement of oxaziranes **9** and **10** to imines, azetines lacking abstractable hydrogens next to nitrogen were chosen as a source for synthesis of the unknown 1-aza-5-oxabicyclo[2.1.0]pentane ring system. Reaction of 2-methoxy-4,4-dimethylazetine **15a** with 1 equiv of MCPBA results in a 50% conversion of **15a** into methyl 3-methyl-3-nitrosobutanoate **17a,** a bright blue liquid. The novel 2,2-dimethyl-4-methoxy-1-aza-5-oxabicyclo[2.1.0]pentane (**16**) was detected as an intermediate in the reaction by observation of characteristic nmr signals at low temperature. An AB pattern for the ring methylene group, the nonequivalent methyl groups, and the upfield methoxy group strongly support the oxazirane structure **16** for this intermediate. It could not be isolated,



however, because of its rapid oxidation on to the nitroso ester, **17a.** In contrast, the reaction of 2-methoxy-3,3,4,4-tetramethylazetine (**18a**) with 1 equiv of MCPBA yields 2-methoxy-4,4,5,5-tetramethyloxazoline (**19a**) with only a trace of methyl 2,2,3-trimethyl-3-nitrosobutanoate (**20**). Following the reaction by low-temperature nmr showed the buildup of **19a** at the expense of azetine **18a,** with no detectable intermediate. Oxidation of 2-methoxy-3,4,4-tri-



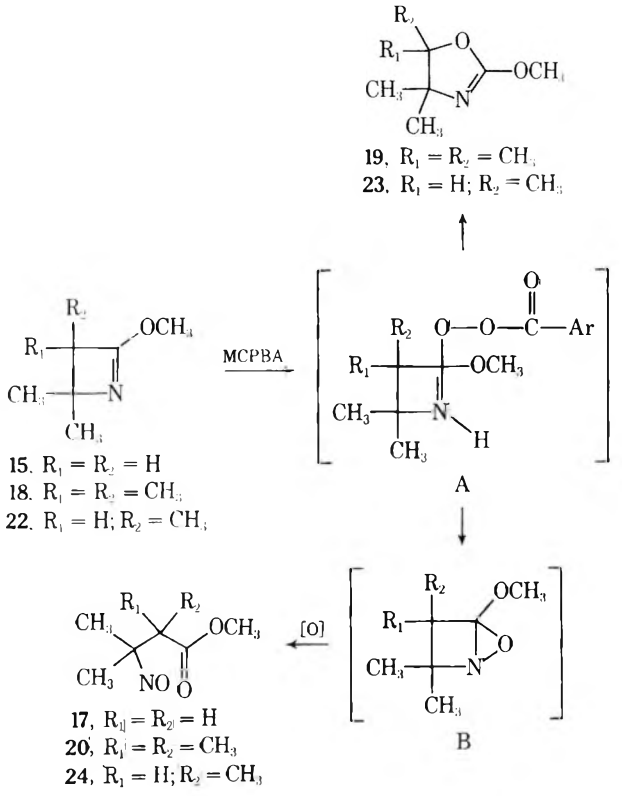
methylazetine (**22**) with an excess of MCPBA results in a mixture of 2-methoxy-4,4,5-trimethyloxazoline (**23**) and methyl 2,3-dimethyl-3-nitrosobutanoate (**24**). A 53% yield of products containing 73% of **23** and 27% of **24** is obtained.



Again, no intermediate oxazirane could be detected by low-temperature nmr. The distribution of oxidation products changes in regular fashion with increasing substitution at C-3. Ring expansion (giving oxazolines) becomes less competitive compared to oxidation to bicyclic oxaziranes (giving nitroso esters) with decreasing substitution at C-3 of the alkoxyazetines. Not only is the bicyclic oxazirane **16** the first reported 1-aza-5-oxabicyclo[2.1.0]pentane ring system, but the oxazolines **19** and **23** represent the first isolated products attributable to a Baeyer–Villiger oxidation of

an imine. The migratory aptitude of C-3 in forming the oxazolines is tertiary > secondary > primary.

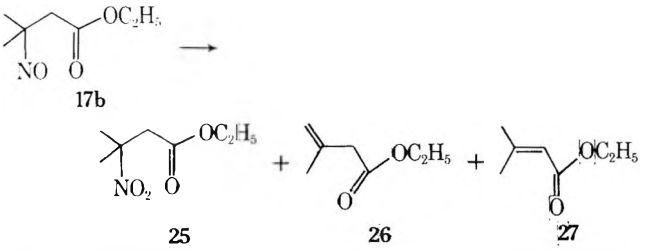
Unlike the one-step mechanism of oxidation of olefins to epoxides,[55] the mechanism of peracid oxidation of imines has recently been proposed to be a two-step mechanism similar to the Baeyer–Villiger reaction.[29] Addition to the carbon nitrogen double bond is normally the rate-determining step. Previous support for this mechanism comes from isolation of intermediates that decompose to oxaziranes[23,24] and products attributable to hydrolysis of Baeyer–Villiger intermediates.[30] The peracid oxidation of azetines **18** and **22** supports this mechanism since the Baeyer–Villiger rearrangement products **19** and **23** are well explained by the intermediacy of the tetrahedral addition product A. The Baeyer–Villiger intermediate A can then decompose competitively to B or **19** (**23**) depending upon the migratory aptitude of C-3.



19, $R_1 = R_2 = CH_3$
23, $R_1 = H$; $R_2 = CH_3$
15, $R_1 = R_2 = H$
18, $R_1 = R_2 = CH_3$
22, $R_1 = H$; $R_2 = CH_3$
17, $R_1 = R_2 = H$
20, $R_1 = R_2 = CH_3$
24, $R_1 = H$; $R_2 = CH_3$

To check for the possibility of Baeyer–Villiger reactions with other imino ethers with tertiary migrating groups, imino ether 2 was oxidized (*vide supra*). No indication of a Baeyer–Villiger product could be found by nmr, however. Apparently migration is dependent on ring strain as well as the availability of a good migrating group. As a point of interest, oxidation of **3** proceeds without the filterable precipitate characteristic of all other peracid oxidations. It could be that a relatively stable Baeyer–Villiger intermediate forms and remains in solution.

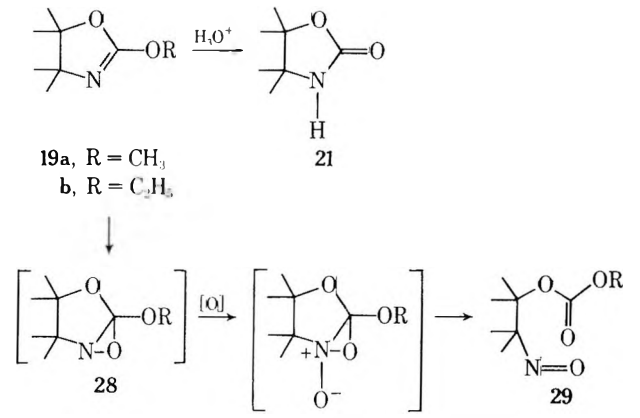
The isolated tertiary nitroso esters encountered in this work decompose on standing. The decomposition was studied using ethyl 3-methyl-3-nitrosobutanoate (**17b**) obtained by double oxidation of azetine **15b.** The nitroso ester **17b** decomposes to a mixture composed of 24% ethyl 3-methyl-3-nitrobutanoate (**25**), 32% of ethyl 3-methyl-3-butenoate (**26**), and 44% of ethyl 3-methyl-2-butenoate (**27**). The formation of nitro compounds from oxaziranes is not unprecedented. Emmons[4] obtained 7% of 2-methyl-2-nitroheptane as the only isolated product from acid hydrolysis of 2-*tert*-octyloxazirane. Also, nitroso compounds are known to form nitroxides plus nitric oxide upon irradiation,[28] to generate olefins plus nitric acid upon thermolysis



17b
25
26
27

with nitric oxide,[56] and to form nitro compounds by disproportionation.[51a] The details of the decomposition pathways of nitroso compounds, however, are unknown. For the above decomposition mixture, a 45 to 55% ratio of **26** to **27** was found. No change in the ratio of products occurred when the unsaturated ester mixture was subjected to experimental conditions.[57]

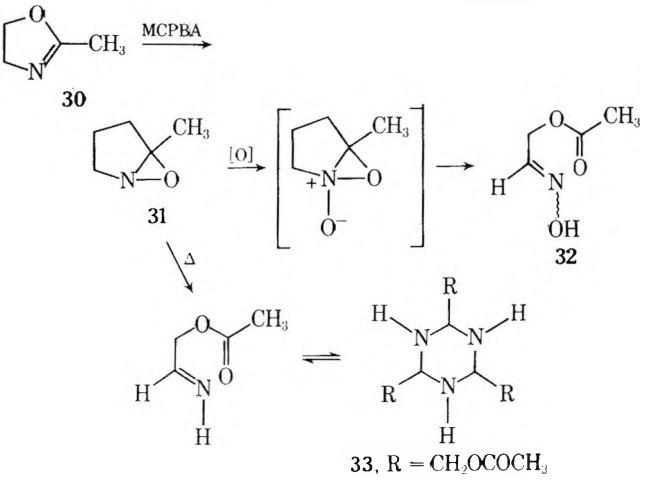
The oxazolines **19a** and **b** formed from oxidation of the azetines are comparable to the imino ethers in reactivity. They were found to undergo hydrolysis and oxidation reactions characteristic of cyclic imino ethers. Acid hydrolysis of **19a** results in the formation of 4,4,5,5-tetramethyl-2-oxazolidinone (**21**). Oxidation of **19b** with 1 equiv of MCPBA results in a 50% conversion of **19b** into the nitroso carbonate **29b,** by a mechanism analogous to that for the oxidation of **15a** to **17a.** The extra alkoxy substituent in **19b**



19a, R = CH_3
b, R = C_2H_5
21
28
29

makes it less reactive than imino ether **7**; **19b** is oxidized only at 25° while **7** reacts with MCPBA below 0°. No intermediate oxazirane was detected in the nmr spectrum at 25° as **19b** was oxidized to **29b.**

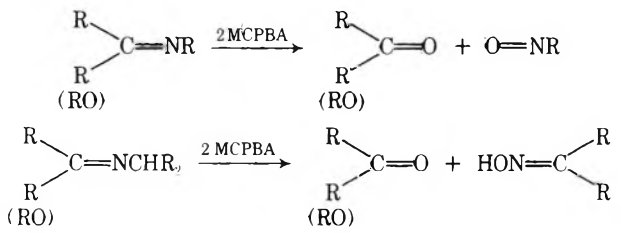
To test the effect of constraining the ether group of an imino ether within a rigid ring, the oxidation of oxazoline **30** was explored. Using 1 equiv of MCPBA, oxidation of **30** followed by vacuum distillation gave a mixture of **30** and 5-methyl-1-aza-4,6-dioxabicyclo[3.1.0]hexane (**31**). No conditions were found, however, where **30** could be completely oxidized to **31** without concurrent formation of 2-acetoxy-



30
31
32
33, R = CH_2OCOCH_3

acetaldoxime (32). The oxazirane 31 decomposes in solution to the trimer of 2-acetoxyacetaldimine (33) in a reaction analogous to the other bicyclic oxaziranes with abstractable hydrogens.

For all of the imino ethers studied, the further oxidation of oxaziranes to give cleavage products is possible. For the imino ethers and the oxazolines **19a,b** the oxidation rates of the oxaziranes and the starting imines are comparable. Whether the oxidation rate of the oxazirane is slow enough to permit its isolation varies rather unpredictably. Imino ethers **1, 2, 3, 7, 8, 15a,** and **30** give isolable (or detectable) oxaziranes but **22** and **19a** give oxidative cleavage products. Such oxidative cleavages appear to be general for imines,[4,5,9,14] imino ethers, and oxazolines. They provide a specific, mild, and nonhydrolytic method for the cleavage of C=N bonds which could be useful synthetically.



Experimental Section

All boiling points and melting points are uncorrected. Vpc analyses were performed with a Varian Aerograph (A-700) gas chromatograph equipped with a thermal conductivity detector. Ir spectra were obtained in solution with a matched reference cell on a Perkin-Elmer 337 grating infrared spectrophotometer. Uv spectra were recorded on a Cary 15 spectrophotometer. Nmr spectra were obtained on a 60-MHz Varian Associates T-60 or a Jeolco C-60H spectrometer. Where indicated, 100-MHz spectra were obtained on a Varian HA-100 spectrometer. Mass spectra were obtained on a MS-902 spectrometer or on a Finnigan 1015 quadrupole spectrometer where indicated.

Materials. The *m*-chloroperbenzoic acid (MCPBA), 1-aza-2-methoxycycloheptene (8), 2-methyloxazoline (30), chlorosulfonyl isocyanate (CSI), and methyl fluorosulfonate were purchased from Aldrich Chemical Co. The amide precursors were either available commercially or made from the corresponding acid chloride and amine for the acyclic amides or chlorosulfonyl isocyanate addition to olefins followed by reduction to the corresponding β-lactams.[45,46]

General Procedure for Preparation of Imino Ethers. To a solution of 1 equiv of trialkyloxonium tetrafluoroborate[40] in dichloromethane was added a solution of amide in dichloromethane at room temperature. After a minimum of 1 hr, this solution was dripped into ice-cold aqueous sodium hydroxide solution, separated, and dried over sodium hydroxide pellets. The solvent was removed by distillation followed by distillation of the imino ether.

O-**Methyl-***N-tert*-**butylformimidate (1):** 70% yield; bp 90–100°; ir (CH_2Cl_2) 2960, 1670, 1370, 1190, 1170, 690 cm^{-1}; nmr (CCl_4) δ 1.15 (s, 9 H), 3.50 (s, 3 H), 7.33 (s, 1 H); mass spectrum (70 eV) *m/e* 115.0997 (calcd for $C_6H_{13}NO$, 115.0997), *m/e* (rel intensity) 115 (M^+, 84), 101 (5), 100 (10), 86 (4), 4 (3), 72 (10), 68 (15), 60 (12), 57 (30), 56 (11), 43 (4), 42 (15), 41 (40), 39 (10), 30 (4), 29 (18), 28 (12), 27 (8), 18 (9), 15 (9).

O-**Methyl-***N-tert*-**butylacetimidate** (3)**:** 80% yield; bp 60° (100 mm); ir (CH_2Cl_2) 2960, 1690, 1370, 1200, 1065 cm^{-1}; nmr (CH_2Cl_2) δ 1.17 (s, 9 H), 1.88 (s, 3 H), 3.44 (s, 3 H); mass spectrum (70 eV) *m/e* 129.1154 (calcd for $C_7H_{15}NO$ 129.1154), *m/e* (rel intensity) 129 (M^+, 15), 115 (6), 114 (100), 82 (6), 74 (17), 73 (11), 72 (9), 58 (5), 57 (32), 56 (11), 55 (5j, 43 (31), 42 (53), 41 (32), 39 (11), 29 (19), 28 (9), 27 (9), 15 (13).

1-Aza-2-methoxycyclopentene (7a): 69% yield; bp 118–120° (lit. bp 118–120°).[58]

1-Aza-2-ethoxycyclopentene (7b): 81% yield; bp 137–142° (lit. bp 135–140°).[59]

2-Methoxy-4,4-dimethylazetine (15a): 78% yield; bp 50° (75 mm) (lit. bp 112–114°).[43]

2-Ethoxy-4,4-dimethylazetine (15b): 81% yield; bp 137–142° [lit. bp 82° (100 mm)].[43]

2-Methoxy-3,3,4,4-tetramethylazetine (18a): 58% yield; bp 54° (28 mm); ir (CH_2Cl_2) 2960, 1630 cm^{-1}; nmr (CCl_4) δ 1.07 (s, 6 H), 1.12 (s, 6 H), 3.66 (s, 3 H); mass spectrum (70 eV) *m/e* 141.1158 (calcd for $C_8H_{15}NO$, 141.1154), *m/e* (rel intensity) 141 (M^+, 49), 140 (14), 127 (34), 99 (15), 85 (18), 84 (44), 83 (13), 73 (13), 70 (45), 69 (70), 68 (18), 58 (20), 57 (18), 56 (33), 55 (26), 43 (30), 42 (70), 41 (100), 39 (36), 29 (18), 28 (30), 27 (25), 18 (31), 15 (27).

2-Ethoxy-3,3,4,4-tetramethylazetine (18b): 80% yield; bp 68° (80 mm) [lit. bp 82° (50 mm)].[43]

2-Methoxy-3,4,4-trimethylazetine (22): 50% yield; bp 50° (50 mm); ir (CCl_4) 2960, 1630 cm^{-1}; (CCl_4) δ 1.05 (d, J = 7.4 Hz, 3 H), 1.13 (s, 3 H), 1.22 (s, 3 H), 1.65 (q, J = 7.4 Hz, 1 H), 3.72 (s, 3 H); mass spectrum (70 eV) *m/e* 127.0992 (calcd for $C_7H_{13}NO$, 127.0997), *m/e* (rel intensity) 127 (M^+, 20), 126 (6), 112 (32), 98 (20), 84 (38), 82 (6), 71 (26), 70 (16), 58 (38), 57 (8), 56 (100), 55 (44), 54 (18), 43 (12), 42 (34), 41 (54), 39 (28), 29 (20), 28 (40), 27 (34), 18 (6), 15 (28).

O-**Methyl-***N-tert*-**butylpivalimidate (2).** No alkylation took place using oxonium salts and *N-tert*-butylpivalamide. The amide and methyl fluorosulfonate were heated to 90° neat. Upon cooling, crystals developed. The solid was identified as the fluorosulfonic acid salt of imino ether **2:** mp 131–133°; ir (CH_2Cl_2) 2950, 1610 cm^{-1}; nmr (CH_2Cl_2) δ 1.45 (s, 9 H), 1.50 (s, 9 H), 4.50 (s, 3 H). The salt was dissolved in dichloromethane and mixed with concentrated aqueous sodium hydroxide at room temperature for 1 hr. The organic layer was separated and dried over sodium hydroxide pellets, and solvent removed. Distillation gave imino ether **2:** bp 75° (45 mm); ir (CH_2Cl_2) 2960, 1660 cm^{-1}; nmr (CCl_4) δ 1.17 (s, 9 H), 1.20 (s, 9 H), 3.67 (s, 3 H); mass spectrum (70 eV) *m/e* 171.1625 (calcd for $C_{10}H_{21}NO$, 171.1623), *m/e* (rel intensity) 171 (M^+, 1), 157.1466 ($M^+ - CH_2$, 2), 156 (4), 102.0919 ($M^+ - C_5H_9$, 0.7), 100 (2), 95 (4), 84 (2), 82 (3), 73 (9), 68 (32), 67 (11), 57 (26), 56 (29), 55 (12), 42 (74), 41 (100), 39 (28), 32 (20), 31 (21), 29 (22), 28 (36), 27 (17), 18 (11), 15 (15); stereochemistry not established.

General Procedure for Oxidation of Imino Ethers. 2-*tert*-Butyl-3-methoxyoxazirane (4). To a mixture of 2.654 g (0.013 mol)[60] of MCPBA, 500 mg of anhydrous potassium carbonate, and 10 ml of dichloromethane at −40° was added 1.326 g (0.012 mol) of 1 in 3 ml of dichloromethane. After 30 min the solution was filtered at −70°. The residue was rinsed with 2 ml of dichloromethane at −70°. The cold filtrates were poured into cold aqueous sodium bicarbonate containing a small amount of sodium sulfite. The organic layer was separated, washed with saturated sodium chloride solution, and dried over anhydrous potassium carbonate. The solvent was removed by careful distillation through a 10-cm Vigreux column. Vacuum distillation gave 979 mg (65%) of **4:** bp 52° (45 mm); ir (neat) 2970, 1480, 1410, 1370, 1280, 1150, 790 cm^{-1}; nmr (CCl_4) δ 1.08 (s, 9 H), 3.15 (s, 3 H), 5.17 (s, 1 H); mass spectrum (70 eV) *m/e* 131.0946 (131.0946 calcd for $C_6H_{13}NO_2$), *m/e* (rel intensity) 131 (M^+, 0.4), 130 (0.6), 129 (0.8), 116 (2.6), 115 (1.6), 114 (1.8), 101 (8), 100 (14), 76 (16), 75 (11), 56 (90), 55 (90), 43 (10), 42 (27), 41 (100), 40 (9), 39 (30).

Hydrolysis of 4. (a) To a solution of 162 mg (1.24 mmol) of **4** in 0.5 ml dichloromethane were added 266 mg (1.55 mmol) of *p*-toluenesulfonic acid, 23 mg (1.28 mmol) of water, and 9.0 mg of benzene. Integration of the nmr spectrum of the homogeneous solution indicated the presence of 95% methyl formate using benzene as an internal standard. Enough aqueous sodium hydroxide solution was added so that the system was basic. Nmr integration on the organic layer showed 87% of *tert*-butylhydroxylamine to be present. (b) A mixture of 498 mg of **4** and 5 ml of 10% aqueous sulfuric acid was stirred at 0°. Within a few minutes a homogeneous solution was obtained. The acidic solution was evaporated to remove methyl formate identical with an authentic sample: ir (CH_2Cl_2) 1730 cm^{-1}; nmr (CCl_4) δ 3.74 (s, 3 H), 8.04 (s, 1 H). The solution was made basic with sodium hydroxide, extracted two times with 3 ml of dichloromethane, and dried over anhydrous potassium carbonate. The solvent was evaporated *in vacuo* leaving behind 76 mg (23%) of *tert*-butyl hydroxylamine: mp 58–59.5° [lit. mp 64–65°];[4] nmr (CCl_4) δ 1.07 (s).

Oxidation of 4. To a solution of 48.8 mg (0.372 mmol) of **4** in 0.5 ml of dichloromethane was added a solution of 83.5 mg (0.412 mmol)[60] of MCPBA in 1.0 ml of dichloromethane at 0°. Integration of the nmr spectrum after 12 hr at 25° gave 76% of methyl formate, 17.5% of 2-methyl-2-nitrosopropane, and 58.5% of the nitroso dimer using benzene as an internal standard.

Oxidation of *tert*-Butylamine. To 92 mg (1.26 mmol) of frozen (−78°) *tert*-butylamine was added 511 mg (2.52 mmol)[60] of MCPBA. The mixture was slowly allowed to come to room temperature. Vacuum distillation gave a blue liquid, bp <25° (1 mm),

that slowly turned into a white solid. The blue liquid was 2-methyl-2-nitrosopropane:[49] ir (CH_2Cl_2) 1540 cm^{-1}; nmr (CH_2Cl_2) δ 1.20 (s). The white solid was the trans dimer of 2-methyl-2-nitrosopropane: mp 75° (sublimation) [lit. mp 83°[6,61] and 76° (sublimation)[62]]; nmr (CH_2Cl_2) δ 1.57 (s).

Thermolysis of 4. A 100-ml evacuated (10^{-3} mm) bulb containing 68 mg of 4 was heated at 158° for 2 hr. Integration of the nmr spectrum using chloroform as an internal standard gave 6% imino ether, 10% isobutylene, 11% methyl formate, 18% methanol, 7% *N-tert*-butylformamide, and 4% recovered oxazirane 4. The remaining material was unidentified residue.

2,3-Di-*tert*-butyl-3-methoxyoxazirane (5). Following the procedure for 4, treatment of 130 mg (0.76 mmol) of 2 with 155 mg (0.70 mmol)[60] of MCPBA gave 68 mg (36%) of 5: bp <50° (2 mm); ir (CH_2Cl_2) 2950, 1120 cm^{-1}; nmr (CH_2Cl_2) δ 0.97 (s, 9 H), 1.13 (s, 9 H), 3.47 (s, 3 H); mass spectrum (70 eV) *m/e* 157.1459 (calcd for $C_9H_{19}NO$, 157.1466, $M^+ - CH_2O$), *m/e* (rel intensity) 187 (0.008), 172 (0.016), 171 (0.034), 170 (0.034), 157 (1.9), 116 (6.4), 73 (9), 57 (100), 56 (64), 42 (18), 41 (64), 39 (23).

Oxidation of 3. A mixture of 372 mg (1.83 mmol)[60] of MCPBA in 5 ml of dichloromethane containing 1.5 g of anhydrous potassium carbonate was cooled to −50°. To this solution was added 212 mg (1.64 mmol) of 3 in 1 ml of dichloromethane. After 30 min the solution was filtered at −50°. Filtration of the solution was difficult, taking over 1 hr, leaving little *m*-chlorobenzoic acid behind. The blue colored solution was distilled at <25° (2 mm) removing some methyl acetate and 2-methyl-2-nitrosopropane along with dichloromethane. Distillation at <25° (0.1 mm) showed the presence of 5% of 2-*tert*-butyl-3-methyl-3-methoxyoxazirane (6), 17% of methyl acetate, 8% of 2-methyl-2-nitrosopropane, and 5% of imino ether 3. The nmr spectrum of 6 in CH_2Cl_2 showed peaks at δ 1.13 (s, 9 H), 1.75 (s, 3 H), and 3.10 (s, 3 H).

5-Methoxy-1-aza-6-oxabicyclo[3.1.0]hexane (9a). Following the procedure for 4, treatment of 708 mg (3.48 mmol)[60] of MCPBA with 310 mg (3.13 mmol) of 7a gave 75% of 9a in dichloromethane (from integration of nmr spectrum using benzene as an internal standard): bp <25° (0.1 mm); ir (CH_2Cl_2) 2940 cm^{-1}; nmr (CH_2Cl_2) δ 1.40–2.40 (m, 6 H), 2.70–3.20 (m, 2 H), 3.12 (s, 3 H); mass spectrum (Finnigan) (70 eV), *m/e* (rel intensity) 115 (M^+, 0.4), 100 (1.1), 94 (0.9), 88 (1.8), 85 (1.5), 84 (0.9), 59 (1.5), 57 (2.9), 56 (3.3), 55 (2.2), 54 (0.9), 44 (27), 40 (100). The mass spectral sample contained some of the trimer, 11.

The oxazirane 9a decomposed to the imine trimer 11a of methyl 4-iminobutanoate upon standing: ir (CH_2Cl_2) 3300, 2940, 1750 cm^{-1}; nmr (CH_2Cl_2) δ 0.80 (br s, 1 H), 1.60 (m, 2 H), 2.30 (m, 2 H), 3.30 (m, 1 H), 3.48 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 329 ($M^+ - 16$, 0.06), 312 (0.1), 298 (0.08), 269 (0.08), 255 (0.4), 241 (1.2), 228 (0.8), 214 (16), 182 (8), 154 (17), 150 (9), 122 (40), 116 (17), 100 (59), 94 (42), 84 (100), 59 (32), 57 (43), 56 (78), 55 (40), 54 (39), 41 (77). The imine trimer **11a**, an oil, decomposed upon attempted purification *via* distillation or column chromatography.[63]

5-Ethoxy-1-aza-6-oxabicyclo[3.1.0]hexane (9b). Following the procedure for 4, treatment of 487 mg (2.40 mmol)[60] of MCPBA with 263 mg (2.33 mmol) of 7b gave 47.5% (by nmr) of 9b in dichloromethane: bp <25° (0.1 mm); ir (CH_2Cl_2) 2970 cm^{-1}; nmr (CCl_4) δ 1.12 (t, J = 7.4 Hz, 3 H), 1.30–2.30 (m, 4 H), 2.80–3.30 (m, 2 H), 3.52 (q, J = 7.4 Hz, 2 H); mass spectrum (Finnigan) (10 eV) *m/e* (rel intensity) 129 (M^+, 0.9), 115 (0.6), 114 (1.1), 113 (1.1), 112 (1.4), 102 (6.4), 101 (100), 100 (13), 86 (27), 85 (68), 84 (52), 74 (29), 73 (70), 58 (22), 57 (41), 56 (67), 46 (55), 45 (27), 44 (27), 42 (22).

The oxazirane 9b decomposed in acid-free dichloromethane solution to the trimer of ethyl 4-iminobutanoate (**11b**) in quantitative yield by nmr: mp 70–72°; ir (CH_2Cl_2) 3400, 2970, 1740, 1180 cm^{-1}; nmr (CH_2Cl_2) δ 0.80 (br s, 1 H, N–H), 1.22 (t, J = 8.5 Hz, 3 H), 1.80 (m, 2 H), 2.30 (m, 2 H), 3.55 (m, 1 H), 4.10 (q, J = 8.5 Hz, 2 H) (*ca.* 7.8, br s, N–H unknown, trace);[63] mass spectrum (70 eV) *m/e* (rel intensity) 387 (M^+, 0.003), 362 (0.01), 343.2175 ($M^+ - C_2H_5O$, 0.003), 326.1851 ($M^+ - C_2H_7NO$, 0.13), 325 (0.3), 297 (0.1), 283.1657 ($M^+ - C_4H_{10}NO_2$, 0.9), 270.1617 ($M^+ - C_5H_9NC_2$, 0.9), 269 (1.3), 256 (0.8), 242 (4), 212 (1.4), 196 (6), 168 (12), 150 (3), 130 (4), 129 (4), 122 (17), 102 (20), 100 (79), 94 (28), 85 (42), 84 (100), 74 (36), 73 (20), 57 (22), 56 (86), 55 (28), 54 (20), 45 (28), 41 (42). The imine trimer **11b** was further characterized by conversion to the 2,4-dinitrophenylhydrazone, mp 113–115° (lit. mp 110–111°),[64a,b] and the semicarbazone, mp 133–135° (lit. mp 135°),[64a,b,65] of ethyl 4-oxobutanoate. The imine trimer **11b** was also converted to its oxime, ethyl 4-isonitrosobutanoate, upon treatment with hydroxylamine (identical ir and nmr with the compound isolated below).

Ethyl 4-Isonitrosobutanoate from Oxidation of 7b. Aqueous sodium bicarbonate solution and dichloromethane were added to the residue from oxidation of **7b** after filtration. The dichloromethane extract was dried over potassium carbonate and evaporated *in vacuo* leaving an oil. Vacuum distillation gave 10 mg of oxime: bp 60–80° (0.3 mm) [lit. bp 139° (14 mm)[65] and 149–152° (11 mm)[66]]; ir (CH_2Cl_2) 3590, 3300, 2970, 1740, 1175 cm^{-1}; nmr (HA-100) (CCl_4) δ 1.27 (t, J = 7.0 Hz, 3 H), 2.49 (m, 4 H), 4.09 (q, J = 7.0 Hz, 2 H), 6.67 (m, 0.39 H, syn), 7.37 (m, 0.61 H, anti), 8.95 (br s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 128 ($M^+ -$ 17.5), 115 (2), 100 (20), 99 (7), 82 (23), 72 (11), 55 (14), 54 (16), 44 (13), 29 (30), 28 (32), 27 (21), 18 (100), 17 (29). The oxime was further characterized by conversion to 2,4-dinitrophenylhydrazone of ethyl 4-oxobutanoate, mp 108–109° (lit. mp 110–111°).[64a,b] Oxidation of **9b** using MCPBA also produced some ethyl 4-isonitrosobutanoate.

Ethyl 4-Oxobutanoate from the Oxidation Products of 7b. Some traces of aldehyde have been observed from neutral hydrolysis of oxazirane **9b**, or acid hydrolysis of the oxime and imine trimer **11b**. The data for the aldehyde are bp 60° (1–2 mm) [lit. bp 84–85° (12 mm)[65]]; ir (CH_2Cl_2) 2940, 2900, 2830, 2730, 1730 cm^{-1}; nmr (CH_2Cl_2) δ 1.16 (t, J = 7.3 Hz, 3 H), 2.64 (four-peak m, 4 H), 4.12 (q, J = 7.3 Hz, 2 H), 9.70 (t, J < 1 Hz, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 115 (M^+, 1.2), 114 (2), 101 (10), 73 (3), 59 (3), 57 (2), 56 (2.5), 55 (6), 45 (4), 44 (2.5), 43 (2.5), 29 (7), 28 (18), 27 (4), 18 (100), 17 (24).

Hydrolysis of Oxazirane 9b. A mixture of 120 mg (1.05 mmol) of oxazirane **9b**, 1 ml of dichloromethane, and 1 drop (19 mg, 1.05 mmol) of water was saturated with hydrogen chloride gas. A water soluble oil remained after removal of volatiles *in vacuo*. The oil was dissolved in deuterium oxide and made basic (pH 8) with sodium hydroxide. The nmr spectrum of the aqueous solution showed the presence of both methyl 4-hydroxyaminobutanoate (**14**) and *N*-hydroxypyrrolidone (**13**). The aqueous material was extracted with dichloromethane. The dichloromethane solution was separated and evaporated *in vacuo*. Water was added (for hydrogen exchange) and reevaporated *in vacuo* leaving 24 mg (17%) of ester hydroxylamine **14**: ir (CH_2Cl_2) 3670, 3570, 3440, 3270, 2940, 1735, 1185 cm^{-1}; nmr (CH_2Cl_2) δ 1.92 (m, $J \simeq$ 6.8 Hz, 2 H), 2.34 (m, 2 H), 2.90 (J = 6.6 Hz, 2 H), 3.64 (s, 3 H), 6.37 (br s, 2 H); mass spectrum (70 eV) *m/e* 130.0873 (calcd for $C_6H_{12}NO_2$, 130.0868), *m/e* (rel intensity) 130 ($M^+ -$ OH, 1.8), 115.0759 ($M^+ -$ NHOH, 1.8), 100 (4.4), 99 (1.8), 55 (3.3), 54 (3), 45 (3.3), 44 (3.7), 43 (3.7), 42 (3), 41 (3.3), 31 (2.6), 29 (10), 28 (11), 27 (6), 18 (100), 17 (26). The ester hydroxylamine 14 decomposed within hours either neat or in solution. The basic aqueous (D_2O) layer above was evaporated *in vacuo* and water was added (for hydrogen exchange), and the mixture reevaporated *in vacuo*, leaving a solid behind. Recrystallization of the solid from carbon tetrachloride–dichloromethane solution gave 28 mg (27%) of hydroxamic acid **13**: mp 80–81° (lit. mp 68–69°);[67] ir (CH_2Cl_2) 3650, 3100, 2900, 1690 cm^{-1}, nmr (CH_2Cl_2) δ 1.67–2.67 (m, 4 H), 3.57 (t, J = 7.0 Hz, 2 H), 8.75 (s, 1 H); mass spectrum (70 eV) *m/e* 101.0470 (calcd for $C_4H_7NO_2$, 101.0476), *m/e* (rel intensity) 101 (M^+, 42), 85 (15), 73 (9), 56 (23), 55 (15), 46 (66), 45 (21), 42 (23), 41 (17), 30 (15), 29 (11), 28 (70), 27 (19), 18 (100), 17 (21).

Oxidation of 8. A mixture of 280 mg (1.38 mmol)[60] of MCPBA, 100 mg of potassium carbonate, and 2 ml of dichloromethane was cooled to −40°. To this mixture was added 143 mg (1.0 mmol) of 8 in 1 ml of dichloromethane. After 30 min the solution was filtered at −78°. The nmr spectrum of this solution indicated approximately 50% formation of 7-methoxy-1-aza-8-oxabicyclo[5.1.0]octane **10** and 50% of a mixture of esters. Distillation afforded 15 mg (1%) of **10**: bp <50° (0.03 mm) [lit. bp 110–120° (0.27 mm)[22]]; ir (CCl_4) 2940, 1480, 1450, 1395, 1320, 1245, 1110 cm^{-1}; nmr (CCl_4) δ 1.15–2.50 (m, 10 H], 3.10 (s, 3 H); mass spectrum (25 eV) *m/e* (rel intensity) 143 (M^+, 0.09), 142 (0.14), 127 (0.9), 126 (1.1), 113 (5), 112 (2), 96 (5), 85 (10), 84 (29), 83 (5), 70 (5), 69 (20), 68 (8), 67 (9), 60 (3), 59 (8), 57 (12), 56 (100), 55 (83), 54 (12), 45 (4), 44 (6), 43 (26), 42 (57), 41 (86). Cyclohexane was an impurity in the mass spectrum. Aqueous sodium bicarbonate–sodium sulfite solution and dichlormethane were added to the residue from distillation of **10**. The dichloromethane extract was dried over potassium carbonate and evaporated *in vacuo* leaving an oil. Distillation afforded 124 mg (78% based on oxime), bp <120° (0.1 mm), of a mixture of methyl 5-cyanopentanoate (**35**) (~35% by nmr) and methyl 6-isonitrosohexanoate (**36**) (~65% by nmr). Redistillation resulted in an early fraction composed of **35** and a late fraction composed of **36**. The data for **35** are bp 60° (0.3 mm) [lit. bp 87–89° (2 mm)[68]]; ir (CCl_4) 2950, 2250, 1750 cm^{-1}; nmr (CCl_4) δ 1.50–2.00 (m, 4 H), 2.00–2.50 (m, 4 H), 3.68 (s, 3 H); mass spectrum (70 eV) *m/e* (rel

intensity) 141 (M^+, 0.4), 139 (1), 110 (24), 83 (5), 82 (60), 81 (8), 74 (90), 69 (8), 68 (24), 59 (87), 55 (100), 54 (33), 53 (12), 43 (40), 42 (29), 41 (78), 39 (33). The data for **36** are bp 120° (0.1 mm); ir (CCl_4) 3580, 3250, 2930, 2850, 1745 cm^{-1}; nmr (CCl_4) δ 1.40–2.00 (m, 4 H), 2.00–2.50 (m, 4 H), 3.65 (s, 3 H), 6.67 (t, J = 5.5 Hz, 0.42 H, anti), 7.36 (t, J = 6.0 Hz, 0.57 H, syn), 8.70 (br s, 1 H); mass spectrum (70 eV) m/e (rel intensity) 143 (M^+ − 16,0.2), 110 (22), 82 (25), 74 (41), 68 (9), 59 (28), 55 (31), 54 (9), 43 (38), 42 (22), 41 (25), 39 (13), 29 (16), 28 (22), 27 (16), 18 (100), 17 (22), 15 (19).

The oxazirane **10** decomposed in acid-free dichloromethane solution to methyl 6-iminohexanoate **12**,[22] apparently a mixture of monomer and trimer from nmr data. The spectral data for **12** are ir (CCl_4) 3300, 2930, 2850, 1745, 1650 cm^{-1}; nmr (CCl_4) δ 1.33–2.00 (m, 6 H), 2.00–2.60 (m, 2 H), 3.06–3.42 (m, 1 H), 3.64 (s, 3 H), 1.20 and 5.40 (two br s, 1 H, N–H, trimer and monomer[63]).

Oxidation of 30. To a solution of 647 mg (3.18 mmol)[60] of MCPBA in 15 ml of dichloromethane was added 239 mg (2.81 mmol) of **30** in 5 ml of dichloromethane; the mixture was left at room temperature for several hours. Removal of solvent *in vacuo* and distillation at <25° (1 mm) gave approximately 100 mg of a mixture of **30** (60% by nmr) and 5-methyl-1-aza-4,6-dioxabicyclo-[3.1.0]hexane **31** (40% by nmr) [nmr (CH_2Cl_2) δ 1.77 (s, 3 H), 2.83–4.00 (m, 4 H)]. The oxazirane **31** decomposed in the above solution to the imine trimer of 2-acetoxyacetaldimine **33**. The volatile imino ether **30** was removed *in vacuo* leaving the imine trimer **33** behind: ir (CH_2Cl_2) 3410, 3300, 2940, 2870, 1740, 1500, 1370, 1230, 1045 cm^{-1}; nmr (CCl_4) δ 1.40 (br s, 1 H), 2.04 (s, 3 H), 3.50–3.84 (m, 1 H), 3.95 (br s, 2 H); mass spectrum (70 eV) m/e 230.1141 (calcd for $C_9H_{16}N_3O_4$, 230.1141), m/e (rel intensity) 230 (M^+ − CH_2OCOCH_3, 1), 215 (3), 186 (1), 173 (1), 144 (5), 129 (15), 119 (2), 117 (2), 114 (2), 113 (1), 112 (1), 102 (9), 84 (8), 83 (16), 72 (20), 71 (6), 70 (8), 60 (18), 59 (7), 57 (8), 45 (11), 44 (8), 43 (100), 42 (17), 41 (6).

Aqueous sodium bicarbonate (containing some sodium sulfite) and dichloromethane were added to the residue from the distillation of oxazirane **30**. The organic layer was separated, dried over potassium carbonate, and evaporated *in vacuo*. The oil residue was distilled, giving 36 mg of 2-acetoxyacetaldoxime **32**: bp ~85° (5 mm); ir (CCl_4), 3575, 3320, 2940, 1750, 1445, 1380, 1230, 1050, 950 cm^{-1}; nmr (CCl_4) δ 2.05 (s, 3 H), 4.57 (d, J = 5.8 Hz, 2 H), 7.37 (t, J = 5.8 Hz, 1 H) for the syn isomer (57%); δ 2.07 (s, 3 H), 4.80 (d, J = 3.8 Hz, 2 H), 6.68 (t, J = 3.8 Hz, 1 H) for the anti isomer (43%); *ca.* 8.0 (br s, 1 H, OH); mass spectrum (70 eV) m/e 100.0397 (calcd for $C_4H_6NO_2$, 100.0398), m/e (rel intensity) 100 (M^+ − OH,0.3), 99.0320 (M^+ − H_2O,0.5), 75 (3), 61 (2), 60 (3), 58 (3), 57 (42), 45 (1.7), 44 (5), 43 (100), 42 (6), 41 (4), 40 (8), 39 (1), 31 (2.5), 30 (2.5), 29 (5), 28 (22), 27 (8), 26 (1.5), 18 (35), 17 (7), 15 (23).

Oxidation of 15a. Some carbon tetrachloride was frozen above a solution of 50 mg (0.44 mmol) of **15a** in 0.3 ml of dichloromethane in an nmr tube. A solution containing 90 mg (0.44 mmol)[60] of MCPBA in 0.5 ml of dichloromethane was placed above the frozen carbon tetrachloride (nmr tube in −78° bath). The nmr tube was placed in a low-temperature nmr probe at −56° and scanned after the sample was removed from the probe to warm to *ca.* −20° briefly. In successive warmings the concentration of 2,2-dimethyl-4-methoxy-1-aza-5-oxabicyclo[2.1.0]pentane (**16**) reached a maximum of 30% of the total mixture as analyzed by nmr (HA-100) [δ 1.11 (s, 3 H), 1.29 (s, 3 H), 2.16 and 2.34 (AB, J = 11 Hz, 2 H), 3.19 (s, 3 H)]. The concentration of **16** decreased and the concentration of methyl 3-methyl-3-nitrosobutanoate **17a** increased as the sample was warmed further. At the completion of the reaction 50% (by nmr) of the imino ether **15a** had been converted to the nitroso ester **17a**: bp <25° (0.1 mm); ir (CH_2Cl_2) 2950, 1740, 1560 cm^{-1}; nmr (CH_2Cl_2) δ 1.25 (s, 6 H), 2.94 (s, 2 H), 3.58 (s, 3 H); mass spectrum (Finnigan) (12 eV) m/e (rel intensity) 129 (M^+ − 16, 2.3) 115 (M^+ − 30, 23), 114 (17), 98 (9), 83 (39), 73 (100), 59 (27), 56 (19), 55 (27), 43 (14), 42 (23), 30 (6), 29 (9), 18 (12), 15 (5). The ion at M^+ − 16 may be due to the parent molecular ion of oxazoline.

Ethyl 3-Methyl-3-nitrosobutanoate (17b). Following the procedure for **4**, treatment of 217 mg (1.72 mmol) of **15b** with 708 mg (3.46 mmol)[60] of MCPBA gave 55 mg (20%) of nitroso ester **17b**: bp <25° (0.1 mm); ir (CCl_4) 2950, 1740, 1560 cm^{-1}; nmr (CCl_4) δ 1.22 (t, J = 7.2 Hz, 3 H), 1.27 (s, 6 H), 2.75 (s, 2 H), 4.07 (q, J = 7.2 Hz, 2 H); mass spectrum (70 eV) m/e (rel intensity) 143 (M^+ − 16, 0.07), 129 (M^+ − 30, 2), 128 (3), 114 (2), 110 (2),3 (9), 59 (8), 57 (7), 56 (12), 43 (12), 42 (8), 41 (9), 39 (7), 31 (11), 28 (8), 27 (13), 18 (100), 17 (23), 15 (6). The nitroso ester **17b** decomposed in carbon tetrachloride at room temperature to 24% (by nmr) of ethyl 3-methyl-3-nitrobutanoate **25**, 3 (by nmr) of ethyl 3-methyl-3-butenoate **26**,[69] and 44% (by nmr) of ethyl 3-methyl-2-butenoate **27**. The data for **25** are bp 60–70° (1 mm); ir (neat) 2980, 1745, 1550, 1380, 1360, 1210 cm^{-1}; nmr (CCl_4) δ 1.27 (t, J = 7.3 Hz, 3 H), 1.68 (s, 6 H), 2.90 (s, 2 H), 4.15 (q, J = 7.3 Hz, 2 H); mass spectrum (70 eV) m/e 130.0504 (calcd for $C_5H_8NO_3$, 130.0504), m/e (rel intensity) 130 (M^+ − OC_2H_5, 8), 129.0917 (M^+ − NO_2, 20), 128.0832 (M^+ − HNO_2, 14), 87 (29), 83.0490 (M^+ − HNO_2 and OC_2H_5, 38), 82 (9), 59 (46), 57 (14), 56 (35), 55 (46), 44 (15), 43 (40), 42 (14), 41 (30), 39 (24), 30 (52), 29 (100), 28 (38), 27 (35), 18 (46), 17 (10), 15 (10). The data for **26** are: bp <25° (1 mm); ir (CCl_4) 1740, 1630 cm^{-1}; nmr (CCl_4) δ 1.20 (t, J = 7.2 Hz, 3 H), 1.75 (s, 3 H), 2.90 (s, 3 H), 4.00 (q, J = 7.2 Hz, 2 H), 4.85 (m, 2 H). The data for **27** are: bp <25° (1 mm); ir (CCl_4) 2950, 1720, 1660, 1450, 1230, 1150 cm^{-1}; nmr (CCl_4) δ 1.20 (t, J = 7.2 Hz, 3 H), 1.83 (d, J = 1.3 Hz, 3 H), 2.08 (d, J = 1.3 Hz, 3 H), 4.00 (q, J = 7.2 Hz, 2 H), 5.50 (heptet, J = 1.3 Hz, 1 H). The α,β-unsaturated ester **27** was independently synthesized from acid hydrolysis of 1-ethoxy-3-methyl-3-hydroxybutyne[70] with 10% sulfuric acid at 25° and shown to have identical nmr and ir spectra.

Attempted Equilibration of Unsaturated Esters 26 and 27. A carbon tetrachloride–dichloromethane solution containing 55% α,β-unsaturated ester **27** and 45% β,γ-unsaturated ester **26** was treated with aqueous hydrochloric acid and sodium nitrite. No change in ester ratio or decomposition occurred during a 2-week test period.

2-Methoxy-4,4,5,5-tetramethyl-2-oxazoline (19a). Following the procedure for **4**, treatment of 200 mg (1.42 mmol) of **18a** with 292 mg (1.44 mmol)[60] of MCPBA gave 100 mg (45%) of oxazoline **19a**: bp 40–60° (0.1 mm); ir (CH_2Cl_2) 2960, 1660, 1350, 1160, 1120 cm^{-1}; nmr (CCl_4) δ 1.08 (s, 6 H), 1.27 (s, 6 H), 3.75 (s, 3 H); mass spectrum (70 eV) m/e 157.1105 (calcd for $C_8H_{15}NO_2$, 157.1103), m/e (rel intensity) 157 (M^+, 2.2), 142 (4.4), 126 (1.2), 110 (4), 99 (12), 98 (12), 85 (8), 84 (100), 73 (3), 69 (6), 56 (16), 43 (9), 42 (14), 41 (22), 39 (10), 28 (9), 27 (10), 26 (7), 18 (5), 15 (24). A trace amount of methyl 2,2,3-trimethyl-3-nitrosobutanoate **20a** was also formed and came over in the distillation of **19a**. The spectral data for **20a** are ir (CH_2Cl_2) 1740 and 1560 cm^{-1}; nmr (CCl_4) δ 0.83 (s, 6 H), 1.55 (s, 6 H), 3.60 (s, 3 H).

Hydrolysis of 19a. Treatment of 111 mg (0.71 mmol) of **19a** in 0.5 ml of dichloromethane with 0.5 ml of 10% sulfuric acid, followed by separation, drying, and evaporation of the organic layer resulted in 15 mg (15%) of 4,4,5,5-tetramethyl-2-oxazolidinone **21**: mp 111–112°; ir (CH_2Cl_2) 3230, 2970, 1760 cm^{-1}; nmr (CCl_4) δ 1.22 (s, 6 H), 1.33 (s, 6 H), (N–H not visible); mass spectrum (70 eV) m/e 143.0948 (calcd for $C_7H_{13}NO$, 143.0946), m/e (rel intensity) 143 (M^+, 1.5), 128 (2.5), 115 (10), 100 (2.5), 84 (13), 59 (29), 57 (14), 43 (9), 42 (28), 41 (10), 39 (5), 29 (4), 28 (6), 27 (4), 18 (100), 17 (25).

2-Ethoxy-4,4,5,5-tetramethyloxazoline 19b. Following the procedure for **4** at −20°, treatment of 168 mg (1.08 mmol) of **18b** with 222 mg (1.09 mmol)[60] of MCPBA gave 103 mg (56%) of oxazoline **19b**: bp 36–38° (0.4 mm); ir (CH_2Cl_2) 2960, 1660, 1380, 1340, 1165, 1130, 1020, 830 cm^{-1}; nmr (CH_2Cl_2) δ 1.18 (s, 6 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.33 (s, 6 H), 4.32 (q, J = 7.2 Hz, 2 H); mass spectrum (70 eV) m/e 171.1264 (calcd for $C_9H_{17}NO_2$, 171.1259) (10 eV), m/e (rel intensity) 171 (M^+, 11), 156 (8), 141 (2), 128 (4), 113 (22), 98 (48), 84 (100), 59 (3), 58 (7), 49 (3), 43 (2). Hydrolysis of oxazoline **19b** also produced oxazolidinone **21**.

Oxidation of 19b. A mixture of 427 mg (2.10 mmol)[60] of MCPBA, 100 mg of potassium carbonate, and 3 ml of dichloromethane was cooled to −30°. To this mixture was added 300 mg (1.75 mmol) of oxazoline **19b** in 3 ml of dichloromethane. After 30 min the solution was allowed to come to room temperature, filtered, and added to an aqueous sodium bicarbonate–sodium sulfite solution. The organic layer was separated and dried over anhydrous potassium carbonate. The nmr spectrum of this solution indicated 40% of ethyl 2-(2,3-dimethyl-3-nitroso)butylcarbonate **29** and 60% starting oxazoline **19b**. Removal of solvent and oxazoline **19b** *in vacuo* followed by bulb-to-bulb distillation, bath 50–100° (0.03 mm), gave 23 mg (16%) of carbonate **29**: ir (CCl_4) 2970, 1740, 1560, 1375, 1280 cm^{-1}; nmr (CCl_4) δ 0.83 (s, 6 H), 1.27 (t, J = 7.2 Hz, 3 H), 2.00 (s, 6 H), 4.07 (q, J = 7.2 Hz, 2 H); mass spectrum (70 eV) m/e 173.1181 (calcd for $C_9H_{17}O_3$, 173.1178), m/e (rel intensity) 173 (M^+ − NO, 2.3), 158 (4), 129 (4), 114 (5), 101 (30), 86 (7), 85 (16), 84 (64), 83 (68), 82 (45), 69 (59), 67 (36), 59 (54), 58 (30), 57 (14), 56 (9), 55 (55), 46 (18), 45 (36), 44 (55), 43 (100), 42 (21), 41 (100), 39 (30), 31 (71), 30 (38), 29 (97), 28 (50), 27 (43), 18 (30), 15 (34).

Oxidation of 22. Following the procedure for **4**, treatment of 288 mg (2.26 mmol) of **22** with 510 mg (2.52 mmol)[60] of MCPBA gave 175 mg (53%) of a mixture of 2-methoxy-4,4,5-trimethyloxazoline (**23**) (73% by nmr) and methyl 2,3-dimethyl-3-nitrosobu-

tanoate (**24**) (27% by nmr). The products were separated by vpc on a 0.25 in. × 6 ft column of 5% SE-30 on 60–80 Chromosorb W. The data for **23** are $T_R(140°)$ = 7.75 min; bp 70° (20 mm); ir (CH_2Cl_2) 2950, 1670, 1470 cm^{-1}; nmr (CH_2Cl_2) δ 1.08 (s, 3 H), 1.21 (s, 3 H), 1.27 (d, J = 6.7 Hz, 3 H), 3.78 (s, 3 H), 4.32 (q, J = 6.7 Hz, 1 H); mass spectrum (70 eV) *m/e* 143.0942 (calcd for $C_7H_{13}NO_2$, 143.0946), *m/e* (rel intensity) 143 (M^+, 9), 129 (5), 128 (60), 100 (6), 85 (8), 84 (100), 73 (10), 71 (8), 70 (5), 69 (7), 59 (10), 58 (22), 56 (25), 55 (11), 49 (7), 43 (19), 42 (21), 41 (26), 39 (12), 30 (8), 29 (13), 28 (25), 27 (16). The data for **24** are: $T_R(140°)$ = 8.50 min; bp <25° (0.1 mm): ir (CH_2Cl_2) 2950, 1735, 1560, 1205 cm^{-1}; nmr (CH_2Cl_2) δ 1.00 (s, 3 H), 1.10 (s, 3 H), 1.18 (d, $J \simeq 7$ Hz, 3 H), 3.64 (s, 3 H), methine hydrogen not detected; mass spectrum (70 eV) *m/e* 129.0909 (calcd for $C_7H_{13}O_2$, 129.0915), *m/e* (rel intensity) 129 ($M^+ - NO$, 21), 128 (14), 113 (14), 100 (6), 97 (11), 88 (21), 83 (7), 74 (7), 73 (100), 71 (7), 70 (36), 69 (50), 68 (7), 67 (7), 59 (50), 58 (7), 57 (13), 56 (21), 55 (43), 53 (14), 45 (9), 44 (21), 43 (36), 42 (28), 41 (79), 40 (11), 39 (28).

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Registry No.—**1**, 49680-36-6; **2**, 49680-48-0; **2** fluorosulfonic acid salt, 52855-94-4; **3**, 52855-95-5; **4**, 49680-37-7; **5**, 49680-50-4; **6**, 52906-79-3; **7a**, 5264-35-7; **7b**, 931-46-4; **8**, 2525-16-8; **9a**, 52855-96-6; **9b**, 49680-39-9; **10**, 35009-23-5; **11a**, 52855-97-7; **11b**, 49680-40-2; **12** monomer, 52855-98-8; **12** trimer, 38167-93-0; **13**, 52928-63-9; **14**, 52855-99-9; **15a**, 23974-38-1; **15b**, 23974-43-8; **16**, 49680-45-7; **17a**, 49680-44-6; **17b**, 52856-00-5; **18a**, 49680-46-8; **18b**, 23974-48-3; **19a**, 49680-47-9; **19b**, 52856-01-6; **20a**, 52856-02-7; **21**, 52856-03-8; **22**, 52856-04-9; **23**, 52856-05-0; **24**, 52856-06-1; **25**, 52856-07-2; **26**, 1617-19-2; **27**, 638-10-8; **29** (R = Et), 52856-08-3; **30**, 1120-64-5; **31**, 52856-09-4; *anti*-**32**, 52856-11-8; *syn*-**32**, 52856-12-9; **33**, 52856-10-7; **35**, 3009-88-9; *anti*-**36**, 42586-30-1; *syn*-**36**, 42586-29-8; MCPBA, 937-14-4; CSI, 1189-71-5; methyl fluorosulfonate, 421-20-5; *N-tert*-butylpivalamide, 686-96-4; methyl formate, 107-31-3; *tert*-butylhydroxylamine, 16649-50-6; *tert*-butylamine, 75-64-9; 2-methyl-2-nitrosopropane, 917-95-3; trans dimer of 2-methyl-2-nitrosopropane, 52856-13-0; ethyl 4-isonitrosobutanoate, 52856-14-1; ethyl 4-oxobutanoate, 10138-10-0; 1-ethoxy-3-methyl-3-hydroxybutyne, 20411-76-1.

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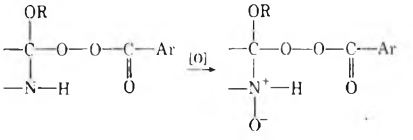

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Mobile Keto Allyl Systems. XVII.[1] Reaction of Amines with β-Carbomethoxy Allyl Bromides

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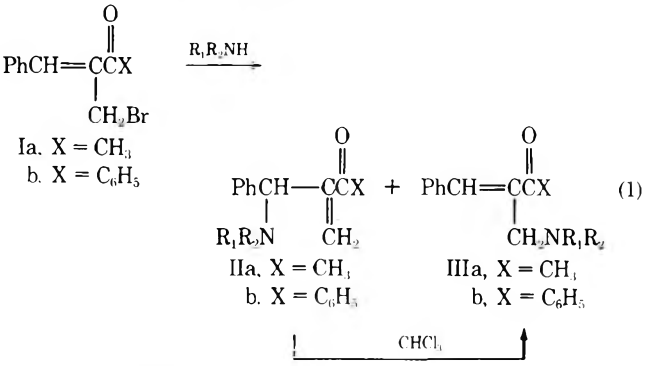
The reaction of a variety of amines with methyl α-(bromomethyl)cinnamate (**1a**) and methyl α-(bromomethyl)-4-chlorocinnamate (**1b**) in hydrocarbon solvent is described. With the exception of *tert*-butylamine, all amines reacted with **1a** or **1b** to produce substitution–rearrangement (**2**) and normal substitution (**3**) products in high yield. The product distribution was strongly dependent on the amine structure. Only **2** was formed upon reaction of *tert*-butylamine with **1a** or **1b**. All examples of **2** isomerized slowly to **3** in chloroform solvent. These reactions are discussed in terms of a variant of an SN2′ mechanism.

We have reported that the reaction of morpholine or piperidine with α-(bromomethyl)benzalacetone (Ia) in hydrocarbon solvent produced substitution–rearrangement (IIa) and normal substitution products (IIIa) in high yield (eq 1).[2] The same amines previously had been found to



react with α-(bromomethyl)chalcone (Ib) to produce substitution–rearrangement products (IIb), exclusively.[3] Compounds II required solvents of higher polarity than hexane or pentane to isomerize to the thermodynamically more stable isomers III.

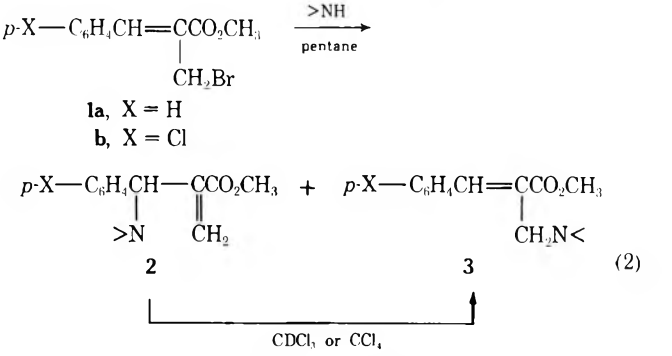
It was rationalized that the initially formed substitution–rearrangement product IIa could compete successfully with Ia for unreacted amine (morpholine or piperidine) to form IIIa. However, IIb did not compete with Ib in pentane for unreacted amine and no normal substitution product IIIb was obtained. The substituent on the β-carbo group of the allyl system in Ia and Ib appears to exert a product controlling factor upon reaction with amines.

We wished to study the reaction of amines with a β-carbomethoxy allyl bromide in hydrocarbon solvent in order to compare methoxy with methyl and phenyl groups as a product controlling factor on the β-carbo group of the allyl system and to study the effect of amine structure on product distribution.

Results

trans-Methyl α-(bromomethyl)cinnamate (**1a**) was synthesized in satisfactory yield by conventional procedures. The product was an oil and had to be distilled twice under vacuum through a Vigreux column to obtain satisfactory purity for this study. *trans*-Methyl α-(bromomethyl)-4-chlorocinnamate (**1b**) was also obtained in good yield and purified by crystallization. Both **1a** and **1b** were sufficiently soluble in pentane to undergo reactions with amines. The solubility of compounds **1** in hydrocarbon solvent is an important consideration when examining reactions with *tert*-butylamine. For example, the para nitro derivative of **1** (X = NO_2) was synthesized and found to be insoluble in pentane. Upon reaction with *tert*-butylamine in acetonitrile, substitution–rearrangement (**2**) and normal substitution (**3**) products were obtained.[4] However, in hydrocarbon solvent, the reaction of *tert*-butylamine with **1a**, **1b**, Ia, and Ib produces the substitution–rearrangement product **2**, exclusively.

The reaction of 2 mol equiv of amine with **1a** or **1b** was carried out in dilute pentane solution at room temperature; the mixture was filtered to remove amine hydrobromide, followed by evaporation of solvent to a small volume and immediate analysis by pmr. In the case of *tert*-butylamine reactions, only one product was formed, while all other amines produced two substitution products. The pentane was evaporated and the resulting oil dissolved in a few milliliters of chloroform-*d* or carbon tetrachloride and allowed to stand at room temperature for several days. Analysis by pmr showed complete isomerization of **2** to **3**.



All examples of **2** and **3** are heat-labile oils which decompose on Florisil or silica gel chromatography columns. The *tert*-butylamino derivatives of **2** and **3** and the 2,5-dimethylpyrrolidine derivative of **3** form stable hydrohalide salts. All the other amino hydrohalide derivatives of **2** and **3** are extremely hygroscopic and had to be elementally analyzed as picrates.

The substitution products are readily distinguished from each other by pmr spectroscopy (Table II). Compounds **2** exhibit three singlets (slightly broadened due to geminal and allylic coupling) assigned to the benzyl and vinylic protons. In **3**, the methoxyl and vinylmethylene singlets are characteristic.

In the case of the morpholine reaction we were able to isolate the picrate of **2c** by repeated crystallization of the picrates derived from the entire reaction mixture. By adding the morpholine slowly over 30 min to **1a**, rather than at once, a 4:1 ratio of **2c** to **3c**, respectively, was obtained as determined by pmr. Fractional crystallization afforded the picrate of **2c** which showed a mixture melting point depression with the picrate of **3c**. A mixture of the two picrates showed two spots when developed on silica gel tlc sheets.

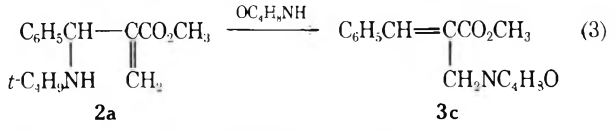
The initially formed substitution–rearrangement prod-

Table I
Amine Reactions with 1a[a]

Amount of substrate, g	Amine	Amount of amine, g	Solvent vol, ml	Reaction time, hr	% Amine HBr	Product(s)
2.57	*tert*-Butylamine	1.50	125	43.5	90.3	**2a**
1.28	Piperidine	0.85	110	1.5	96.4	**2b**:**3b** (79:21)
1.28	Morpholine	0.87	150	54	92.8	**2c**:**3c** (55:45)
1.28	*N*-Methylcyclohexylamine	1.13	150	47	89.7	**2d**:**3d** (67:33)
1.28	2-Methylpiperidine	0.99	200	22	93.3	**2e**:**3e** (25:75)
1.28	2,6-Dimethylpiperidine	1.13	115	25	14.4	Not characterized
2.56	2,5-Dimethylpyrrolidine	1.98	200	26	83.4	**2f**:**3f** (97:3)
1.28	*N*-Methylisopropylamine	0.73	150	42	0	
1.28	Diisopropylamine	1.01	150	50	0	
	Amine Reactions with **1b**[a]					
2.90	*tert*-Butylamine	1.50	125	41	92.3	**2g**
2.90	Piperidine	1.70	200	73	100.0	**2g**:**3g** (48:52)

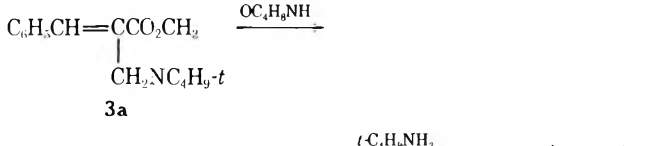
[a] In all the reactions reported here, the substrate:amine mole ratio was exactly 1:2, respectively, in pentane solvent. See Experimental Section for general procedure.

uct **2a** slowly reacted with a slight excess of morpholine in pentane solvent to produce **3c**, quantitatively.



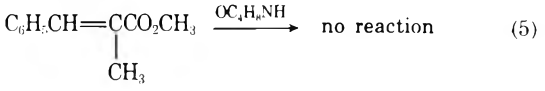
(3)

The same product was also obtained by treating a 7 mol excess of morpholine with **3a** over 13 days in pentane solvent. No evidence for the prior formation of **2c** or a 1,3-diamine was found. In contrast, **3c** did not react with an 8 mol excess of *tert*-butylamine in pentane for 7 days.



(4)

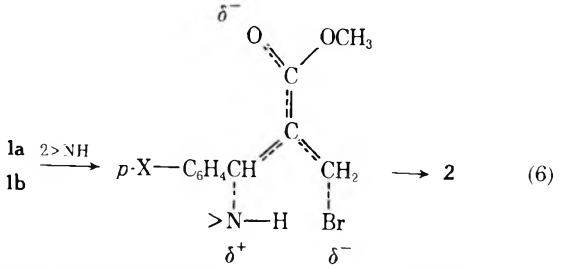
Methyl α-(methyl)cinnamate was dissolved in a 20 mol excess of morpholine without solvent at room temperature for 8 days. After removal of the morpholine, the residue was shown to be unchanged ester by its pmr spectrum.



(5)

Discussion

The formation of rearrangement–substitution products from the reaction of amines with β-carbo allyl halides has been considered to be a variant of an SN2′ mechanism in which carbon–nitrogen bond formation proceeds ahead of carbon–halogen bond breakage.[5] The oxygen atom of the β-carbo group accepts much of the developing negative charge which is ultimately carried by the leaving halide ion. This hypothesis is invoked to explain the formation of compounds **2** from the reaction of amines with **1a** or **1b**.



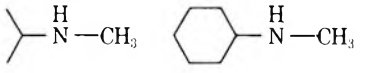
(6)

Prior ionization of allyl halides **1a** and **1b** in hydrocarbon solvent followed by nucleophilic attack on a rearranged carbocation to form **2** should not be very important. The low dielectric constant of pentane and the presence of the electron-withdrawing β-carbo substituent on the allyl system in **1a** and **1b** would depress the formation of a carbocation.[6]

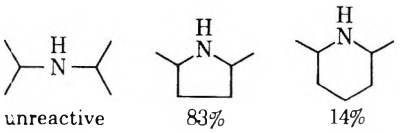
A 1,4-Michael addition of amine to **1a** or **1b** followed by elimination of hydrogen bromide to form **2** is ruled out because morpholine does not react with methyl α-(methyl)cinnamate (eq 5).

Kinetic studies on six amine reactions with Ia showed a rate retardation with increasing bulk at the α-carbon atom of the amine.[5a] Only the abnormal substitution product was obtained (eq 1).

Examination of Table I reveals a wide range of product distribution yields for the reaction of amines with **1a** as a consequence of subtle stereochemical alterations in amine structure. For example, *N*-methylisopropylamine was totally unreactive toward **1a**; however, "pinning" the methyls of the isopropyl group back slightly and forming a cyclohexyl ring results in *N*-methylcyclohexylamine which easily reacts with **1a** under the same conditions.



Diisopropylamine is also unreactive toward **1a**. When its methyl groups are "joined" to construct 2,5-dimethylpyrrolidine, we observe a reaction to 83% completion. If the pyrrolidine ring is increased by one methylene group, the yield is drastically reduced.



The reactivity of amines toward **1a** varied from (a) no reaction, (b) production of rearrangement–substitution product, exclusively, to (c) production of both rearrangement–substitution and normal substitution products. No amine was found which would produce only the normal substitution product in pentane solvent.

Stork and White demonstrated a cis geometry for the attack of piperidine to the leaving group in an SN2′ reaction for *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates.[7] The cis orientation is crowded but can be facilitated by hydrogen bonding of the amine to the carbonyl oxygen atom or the bromide atom (eq 6).[8] The differences in amine reactivity upon reaction with **1a** are best explained in terms of the steric demands of the amine structure rather than by

Table II
60-MHz Proton Magnetic Resonance Data[a]

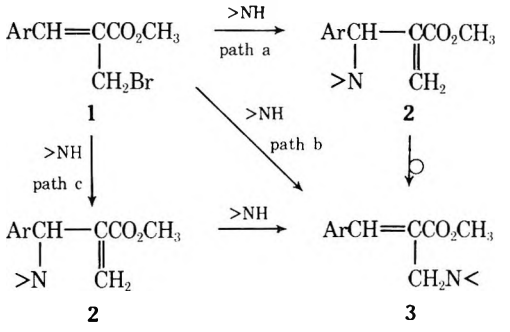
Compd	Aromatic[c]	C_6H_5CH	OCH_3	$C{=}CH_2$	CH_2N	Amino group
2a[b]	6.9–7.3	4.68	3.50	6.05, 6.15		1.05 *t*-C_4H_9
3a[b]	7.2–7.7		3.77		3.44	1.15 *t*-C_4H_9
2b[c]		4.35		6.03, 6.28		
3b[b]	6.95–7.7		3.68		3.22	2.1–2.5 CH_2NCH_2, 1.2–1.7 $(CH_2)_3$
2c[b]		4.25		6.05, 6.30		
3c[b]	7.1–7.7		3.75		3.27	3.4–3.7 CH_2OCH_2, 2.3–2.5 CH_2NCH_2
2d[b]		4.75		6.00, 6.28		
3d[b]	7.2–7.8		3.73		3.40	0.9–2.7 N-CH_3 and cyclohexyl ring
2e[d]		5.00, 5.15[f]		5.98, 6.18[e] 6.40, 6.55[e]		
3e[d]	7.4–8.1		3.97		3.30, 3.70[g]	1.0–3.0 piperidine ring and CH_3
2f[d]		5.08		5.92, 6.37		
3f[d]	7.1–7.8		3.75		3.58	2.3–3.0 CHNCH, 0.8–2.2 pyrrolidine ring, and two CH_3
2g[b]	6.9–7.1	4.68	3.50	5.85, 6.04		1.1 NH, 1.03 *t*-C_4H_9
3g[d]	7.2–7.75		3.80		3.50	2.6 N*H*, 1.03 *t*-C_4H_9
2h[d]		4.30		6.05, 6.35		
3h[d]	7.2–7.8		3.78		3.24	2.2–2.6 CH_2NCH_2, 1.3–1.7 $(CH_2)_3$

[a] Chemical shifts in δ units from internal TMS. All resonances integrated correctly for the proposed structures. [b] Carbon tetrachloride. [c] Pentane. [d] Chloroform-*d*. [e] Benzal proton ($C_6H_5CH{=}C$) resonance masked by aromatic absorption. [f] A pair of singlets due to presence of diastereomers. [g] Diastereotopic protons with J = 12 Hz. See R. E. Lyle, J. J. Thomas, and D. A. Walsh in "Conformational Analysis," G. Chiurdoglu, Ed., Academic Press, New York, N.Y., 1971, pp 157–164.

the basicity of the amine. For example, diisopropylamine is reported to be more basic than morpholine; yet, as stated, it is unreactive toward **1a** while morpholine reacts smoothly.[9]

The formation of normal substitution products **3** can be explained by at least three major pathways (Scheme I).

Scheme I



First, from path a, it is known that all examples of the rearrangement–substitution products **2** slowly isomerize in chloroform or carbon tetrachloride solvent at high concentration (30–50% by volume) to the thermodynamically more stable isomers **3** (eq 3). Qualitatively, the more polar solvent provided a faster rate of rearrangement. This solvent effect has also been observed for the self-rearrangement of **Ib** and considered to be an intramolecular isomerization.[3b] However, the requisite high concentrations in the more polar solvents necessary to effect this isomerization preclude the importance of this pathway for the formation of **3** under the conditions of eq 2.

A second major pathway (path b) to consider involves a direct SN2 substitution mechanism. Indeed, primary allyl halides react with amines to yield mainly normal substitution products.[10] Nevertheless, our data suggest initial attack of amine on the γ-carbon atom of the allyl system in **1**. With *tert*-butylamine, only **2a** was formed. However, when the reaction was carried out with excess amine (>2 mol), then a small amount of **3a** was found. It was also determined that the yield of **3** could be reduced appreciably while increasing the yield of **2** if the amine were slowly dripped into the pentane solution of **1a** rather than an immediate mixing of reactants. These data suggest that the most plausible explanation for the formation of **3** is by path c in Scheme I.

The β-carbo allyl bormide **1** reacts with amine to form **2** initially, which then can react with another molecule of amine to undergo a second rearrangement–substitution process to produce **3**. The possibility of this reaction is demonstrated in eq 3.[11] Compounds **1** and **2** can compete with each other for unreacted amine except when the amine is *tert*-butylamine.

The phenyl ring in **1a** appears to exert a product controlling effect from eq 4. Morpholine reacted quantitatively with **3a** to produce **3c**; however, under the same reaction conditions *tert*-butylamine would not react with **3c**. This further supports the conclusion that attack of an amine on **1** or **2** involves a rearrangement–substitution process which we consider to be a variant of an SN2′ mechanism.

It is interesting to note that in Bordwell's criticisms of the purported concertedness of the SN2′ mechanism, reactions involving bond making proceeding well ahead of bond breaking are "difficult to exclude."[12] Without kinetic data on the reactions of amines with **1** we cannot comment on the concertedness of these reactions.

Experimental Section

Melting points were determined with a Mel-Temp Laboratory Device and are uncorrected. Infrared spectra were collected on Perkin-Elmer Model 237 and 621 spectrophotometers. Nuclear magnetic resonance data were recorded on Varian Models A-60 and A-60D. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Methyl α-(Bromomethyl)cinnamate (1a). A 145-g (0.895 mol) sample of α-(methyl)cinnamic acid,[13] mp 78.5–79° (lit. 81°), in 500 ml of methanol containing *ca.* 0.5 ml of concentrated sulfuric acid was refluxed 5 days. The methanol was evaporated and the residue taken up in ether, washed with water and 10% potassium hydroxide, and again with water. The ethereal layer was dried with mag-

Table III
Elemental Analysis and Infrared Data

Compd	Calculated C	H	N	X[a]	Found C	H	N	X[a]	$\nu_{C=O}$[b]	Mp, °C
2a[c]	63.48	7.81	4.94	12.49	63.58	7.80	4.96	12.61	1710	183.5–184.5
3a[c]	63.48	7.81	4.94	12.49	63.48	7.89	4.99	12.61	1710	14–175.5
3b[d]	54.10	4.95	11.47		54.32	5.07	11.41		1711	134.5–135.5
2c[d]	51.43	4.52	11.42		51.32	4.58	11.34			180–181
3c[d]	51.43	4.52	11.42		51.62	4.71	11.22		1714	172–174
3d[d]	55.81	5.46	10.85		56.01	5.38	10.98		1714	131.5–133
3e[d]	54.98	5.22	11.15		54.85	5.16	11.18		1712	124–126.5
3f[e]	57.61	6.83	3.96	22.57	57.28	6.88	3.79	22.71	1715	170–172
2g[c]	56.60	6.65	4.40	22.28	56.70	6.73	4.21	22.01	1713	178–179
3g[c]	56.60	6.65	4.40	22.28	56.39	6.69	4.24	22.09	1701	198.5–199.5
3h[d]	50.53	4.43	10.72	6.78	50.49	4.46	10.76	6.52	1712	193–194

[a] Where X is bromide or chloride. [b] Free amine calibrated against polystyrene in CCl_4. [c] Hydrochloride. [d] Picrate. [e] Hydrobromide. [f] In $CHCl_3$.

nesium sulfate and the solvent evaporated to leave 96.1 g (61%) of methyl α-(methyl)cinnamate which solidified upon standing: mp 36–37° (lit.[14] 39°); pmr (CCl_4) δ 7.67 (m, 1, C_6H_5CH), 7.2–7.5 (m, 5, aromatic), 4.76 (s, 3, OCH_3), and 2.09 (d, J = 2 Hz, 3, vinyl CH_3); $\nu_{C=O}$ (CCl_4) 1713 cm^{-1}.

An 80-g (0.45 mol) sample of the methyl ester in 200 ml of carbon tetrachloride containing 80 g (0.45 mol) of *N*-bromosuccinimide and *ca.* 0.01 g of benzoyl peroxide was refluxed for 6 hr, cooled to room temperature, and filtered, and the solvent removed *in vacuo* with heating. The residue was distilled through a 6-in. glass Vigreux column and a light yellow oil collected at 100–140° (1–2.5 mm), 92 g (80%). A second distillation provided analytically pure product which was used for reaction with amines: pmr (CCl_4) δ 7.78 (m, 1, C_6H_5CH), 7.25–7.7 (m 5, aromatic), 4.35 (s, 2, CH_2Br), and 3.83 (s, 3, OCH_3); $\nu_{C=O}$ (CCl_4) 1712 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}BrO_2$: C, 51.99; H, 4.36; Br, 31.45. Found: C, 52.03; H, 4.36; Br, 31.51.

Methyl α-(Bromomethyl)-4-chlorocinnamate (1b). α-(Methyl)-4-chlorocinnamic acid was prepared by a previously published procedure in 52% yield, mp 162–165° (lit.[15] 167°). A 37-g (0.186 mol) sample of the acid in 60 g (1.86 mol) of methanol containing 3.0 ml of concentrated sulfuric acid was refluxed 25 hr, cooled to room temperature, and taken up in ether. The ethereal solution was washed with water, saturated sodium bicarbonate, and again with water. The aqueous washings were then extracted with ether, the combined ethereal solutions dried with magnesium sulfate, and the solvent evaporated *in vacuo* with warming to leave 31.7 g (80.5%) of the methyl ester as an oil: pmr (CCl_4) δ 7.4 (m, 1, ClC_6H_4CH), 7.15–7.25 (m, 4, aromatic), 3.67 (s, 3, OCH_3), and 2.0 (d, J = 1.5 Hz, 3. CH_3); $\nu_{C=O}$ (CCl_4) 1718 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26; Cl, 16.84. Found: C, 62.61; H, 5.30; Cl, 17.10.

A 31.7-g (0.149 mol) sample of the methyl ester in 175 ml of carbon tetrachloride containing 26.5 g (0.149 mol) of *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide was refluxed 21 hr and filtered, and the solvent evaporated *in vacuo* with warming to leave a light yellow oil. The oil was taken up in ether–hexane (1:5, v/v) and cooled to induce crystallization of 26.4 g (6.1.2%) of white crystals: mp 35–35.5°; pmr (CCl_4) δ 7.6 (s, 1, ClC_6H_4CH), 7.4 (s, 4, aromatic), 4.26 (s, 2, CH_2Br), and 3.80 (s, 3, OCH_3); $\nu_{C=O}$ (CCl_4) 1724 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}BrClO_2$: C, 45.63; H, 3.48; Br and Cl, 39.84. Found: C, 45.63; H, 3.47; Br and Cl, 39.97.

General Procedure for the Reaction of Amines with 1a and 1b. A small amount of **1a** or **1b** dissolved in pentane was treated at once with 2 mol equiv of amine in a small volume of the same solvent. The mixture was filtered to remove amine hydrobromide, followed by evaporation of solvent *in vacuo* at room temperature to a small volume for analysis by pmr. The solvent was then evaporated completely and the reaction product(s) taken up in carbon tetrachloride or chloroform-*d* and allowed to stand several days for complete isomerization to the normal substitution product which was fully characterized. See Tables I–III for results and data.

Reaction of Methyl α-(α-*tert*-Butylaminobenzyl)acrylate (2a) with Morpholine. A 0.95-g (3.85 mmol) sample of **2a** was dissolved in 10 ml of pentane containing 0.43 g (5.0 mmol) of morpholine. The contents were kept at room temperature for 5 days and analyzed by pmr to show a quantitative conversion to **3c**.

Reaction of Methyl α-(*tert*-Butylaminomethyl)cinnamate (3a) with Morpholine. To a pmr tube containing chloroform-*d* was added a small amount of **3a** and morpholine in a 1:7 mole ratio, respectively. The contents were kept at room temperature 13 days and analyzed by pmr to show complete conversion of **3a** to **3c**.

Attempted Reaction of Methyl α-(Morpholinomethyl)cinnamate (3c) with *tert*-Butylamine. A 0.58-g (2.37 mmol) sample of **3c** dissolved in chloroform-*d* containing 1.20 g (16.5 mmol) of *tert*-butylamine stood at room temperature 153 hr with no reaction observed by pmr.

Attempted Reaction of Methyl α-(Methyl)cinnamate with Morpholine. A 1.65-g (0.01 mol) sample of ester was dissolved in 17.5 ml (0.2 mol) of morpholine and was kept at room temperature for 8 days. The morpholine was evaporated *in vacuo* and the residue analyzed by pmr to show only the starting material.

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Registry No.—**1a**, 53059-43-1; **1b**, 53059-44-2; **2a**, 53059-45-3; **2a** HCl, 53059-46-4; **2b**, 53059-47-5; **2c**, 53059-48-6; **2c** picrate, 53059-49-7; **2d**, 53059-50-0; **2e** isomer a, 53059-51-1; **2e** isomer b, 53059-52-2; **2f**, 53059-53-3; **2g**, 53059-54-4; **2g** HCl, 53059-55-5; **2h**, 53059-56-6; **3a**, 53059-57-7; **3a** HCl, 53059-58-8; **3b**, 53059-59-9; **3b** picrate, 53059-60-2; **3c**, 53059-61-3; **3c** picrate, 53059-62-4; **3d**, 53059-63-5; **3d** picrate, 53059-64-6; **3e**, 53059-65-7; **3e** picrate, 53059-66-8; **3f**, 53059-67-9; **3f** HBr, 53059-68-0; **3g**, 53059-69-1; **3g** HCl, 53059-70-4; **3h**, 53059-71-5; **3h** picrate, 53059-72-6; *tert*-butylamine, 75-64-9; piperidine, 110-89-4; morpholine, 110-91-8; *N*-methylcyclohexylamine, 100-60-7; 2-methylpiperidine, 109-05-7; 2,6-dimethylpiperidine, 504-03-0; 2,5-dimethylpyrrolidine, 3378-71-0; *N*-methylisopropylamine, 4747-21-1; diisopropylamine, 108-18-9; α-(methyl)cinnamic acid, 1199-77-5; methyl α-(methyl)cinnamate, 25692-59-5; *N*-bromosuccimide, 128-08-5; α-(methyl)-4-chlorocinnamic acid, 1202-60-4; methyl α-(methyl)-4-chlorocinnamate, 53059-73-7.

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The Thermal and The Copper-Catalyzed Addition of Sulfonyl Bromides to Phenylacetylene[1]

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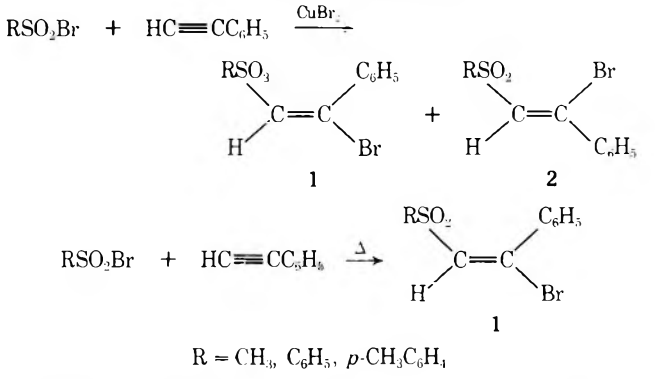
The copper-catalyzed addition of methane-, benzene-, and *p*-toluenesulfonyl bromide to phenylacetylene yields mixtures of trans (1) and cis addition products (2). In contrast, the thermal reaction leads exclusively to 1. In the catalyzed reaction, excess of bromide ions promotes the formation of 1. Both 1 and 2 undergo facile elimination of HBr to give the α-acetylenic sulfone (3). Two distinct mechanisms for the addition reaction are suggested, namely, a trans addition process operating *via* a free-radical chain, and, concurrently, a cis addition process, *via* a concerted reaction mechanism, directed by the copper catalyst.

We previously described the stereoselective, copper-catalyzed 1:1 addition of aliphatic and aromatic sulfonyl chlorides to acetylenes by a free-radical, redox-transfer chain mechanism, yielding mixtures of *trans*- and *cis*-β-chlorovinyl sulfones.[2] In the copper-catalyzed addition of sulfonyl chlorides to phenylacetylene, the course of addition could be controlled by polar factors to give preferentially either trans or cis addition products;[3] no adduct was formed in the absence of copper chloride, in spite of prolonged heating.[2] We now discovered that, in contrast to sulfonyl chlorides, the corresponding bromides undergo addition across the triple bond in the dark, and in the absence of any catalyst, thus demonstrating homolysis of the S–Br bond under mild thermal conditions.

A comparison between the thermal and the copper-catalyzed addition of sulfonyl bromides to phenylacetylene has enabled us to elucidate the specific role of the catalyst in directing the stereochemistry of the addition; such a comparative study could not be performed with sulfonyl chlorides.

This paper presents examples of thermal as well as copper-catalyzed 1:1 additions of methane-, benzene-, and *p*-toluenesulfonyl bromide to phenylacetylene, yielding in the catalyzed process mixtures of trans (1) and cis addition products (2); and in the thermal process exclusively trans addition product (1). Sulfonyl bromides have been used in



synthesis to a much lesser extent than sulfonyl chlorides, even though they are more reactive; they can be made by simple one-step procedures.[4] It is worthwhile mentioning here that sulfonyl iodides are much more reactive, as shown for instance by Truce and Wolf, who described the light-catalyzed trans addition of sulfonyl iodides to acetylenes, leading to β-iodovinyl sulfones.[5] Thus far, alkanesulfonyl iodides have not been isolated owing to their instability, and had therefore to be prepared *in situ*.[5,6] Sulfonyl bromides have the advantage over sulfonyl iodides of being stable compounds, and at the same time being more reactive than the corresponding sulfonyl chlorides.

Only a few β-bromovinyl sulfones have been reported in the literature; their syntheses consist of several steps, in which, for instance, in the final step a bromovinyl sulfide is oxidized to the corresponding sulfone[7] or hydrogen bromide is added to an α-ethynyl sulfone.[8]

A one-step synthesis of β-bromostyryl sulfones by the direct addition of sulfonyl bromides to acetylenes has been reported briefly in two instances.[9,10]

Zakharkin and Zhigareva described recently a thermal addition of benzenesulfonyl bromide to phenylacetylene, leading to a cis addition product.[9] We prove that under such conditions the trans addition product (1) is being formed exclusively (see below).

Results and Discussion

The Copper-Catalyzed Addition. The copper-catalyzed addition of methane-, benzene-, and *p*-toluenesulfonyl bromide to phenylacetylene was performed as described for the addition of sulfonyl chlorides to acetylenes.[2] Like the chlorides, sulfonyl bromides gave mixtures of cis and trans addition products, reacting somewhat faster than the corresponding chlorides. The reaction may be conducted with equimolar amounts of the reactants[11] in an inert solvent such as acetonitrile, at reflux temperatures or preferably in a sealed tube, where rates of reaction could be conveniently followed by dilatometry. The reaction in a sealed tube proved to be cleaner and faster, particularly when degassing removed atmospheric oxygen which resulted in decreased induction periods. Cupric bromide was used in a catalytic amount; lithium bromide, as a source of excess bromide ions, promoted preferential formation of trans addition products, as chloride ions did in the addition of sulfonyl chlorides to phenylacetylene[3] (see Table I, No. 1, 4, and 7). In the absence of additional bromide ions, the reaction was slower, and a higher proportion of cis addition products was formed (see Table I, No. 2, 5, and 8).

The Thermal Addition. Alkyl- and arylsulfonyl bromides were found to add smoothly to phenylacetylene, in the absence of any catalyst or light, affording high yields of a single 1:1 addition product which turned out to be identical with the trans addition product (1) obtained in the copper-catalyzed reaction. No trace of the corresponding cis addition isomer (2) could be detected after careful column as well as thin-layer chromatographic, separations (see Table I, No. 3, 6, and 9).[12]

Configurational Assignments Based on Spectral Data. Structural proof and configurational assignments were based on similar criteria as applied to the characterization of the *trans*- and *cis*-β-chlorostyryl sulfones.[2,3] As mentioned previously,[2] only the cis addition products (2) can accommodate a coplanar conformation. This is impossible for the trans addition products (1), due to steric hin-

Table I
Reactions of Sulfonyl Bromides (10 mmol) with Phenylacetylene (11 mmol) in Acetonitrile (2G) at 100°

No.	RSO_2Br R=	$CuBr_2$, mmol	LiBr, mmol	Time, hr	Conversion, %	Adduct Distribution, % 1	2
1	CH_3	0.2	0.3	6	90	88	12
2	CH_3	0.2		6	86	55	45
3	CH_3			9	90	100	
4	C_6H_5	0.2	0.3	4	90	85	15
5	C_6H_5	0.2		6	92	44	56
6	C_6H_5			6	88	100	
7	p-$CH_3C_6H_4$	0.2	0.3	6	93	83	17
8	p-$CH_3C_6H_4$	0.2		6	88	52	48
9	p-$CH_3C_6H_4$			9	85	100	

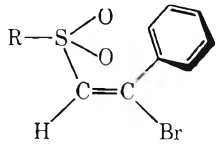
Table II
Ultraviolet Spectra

R	1 Phenyl bands λ_{max}	1 Phenyl bands ϵ	1 Styryl bands λ_{max}	1 Styryl bands ϵ	2 Phenyl bands λ_{max}	2 Phenyl bands ϵ	2 Styryl bands λ_{max}	2 Styryl bands ϵ
CH_3	212	8,000	254	8,000	213	8,000	264	16,000
C_6H_5	211	20,000	258	10,000	213	18,000	276	20,000
p-$CH_3C_6H_4$	209	20,000	238	14,000	219	18,000	273	20,000

Table III
Nuclear Magnetic Resonance Data[a]

R	1 Vinyl protons(s)	1 Methyl protons (s)	1 Phenyl protons (m)	2 Vinyl protons (s)	2 Methyl protons (s)	2 Phenyl protons (m)
CH_3	7.09	2.71 (3 H)	7.37–7.65 (5 H)	7.22	3.21 (3 H)	7.37–7.70 (5 H)
C_6H_5	7.17		7.25–7.65 (10 H)	7.33		7.36–7.70 (8 H) 8.09 (d, 2 H, J = 7.5)[b]
p-$CH_3C_6H_4$	7.15	2.37 (3 H)	7.51 (d, 2 H, J = 8.5)[c] 7.19 (d, 2 H, J = 8.5)[c] 7.40 (m, 5 H)	7.30	2.45 (3 H)	7.97 (d, 2 H, J = 8.5)[c] 7.34 (d, 2 H, J = 8.5)[c] 7.46–7.60 (5 H)

[a] Measured in $CDCl_3$ on a Varian A-60 with TMS as internal standard; chemical shifts reported in δ (ppm) and apparent spin couplings (J) in Hz units; s = singlet, d = doublet, m = multiplet. [b] Phenyl protons ortho to the carbon atom attached to the electronegative sulfone group. [c] Pair of doublets of a typical AA'BB' pattern for a para-disubstituted phenyl ring.



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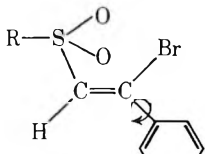


2

drance. The styryl band for the cis addition products (2) absorbs at longer wavelengths, and with much stronger intensity than for the trans isomers (1) (see Table II). The infrared spectra were very much like those of the chloro analogs. In the C=C stretching frequencies region, a strong adsorption peak at 6.19 μ was found to be characteristic for the trans addition products (1), and a strong absorption peak at 6.36 μ was typical for the planar and more conjugated cis addition isomers (2); it was also possible to characterize the structural isomers on the basis of sharp and strong–CH= out-of-plane bending vibrations at 11.3 μ of the trans addition products (1) and at 11.05 μ of the cis addition products (2).

The nmr spectra of the addition compounds were quite similar to those of the chloro analogs.[2,3] The vinylic protons of the bromo adducts were generally more deshielded than those of the corresponding chloro adducts; also, these protons, as well as the methyl proton in 2 (R = CH_3, R = p-$CH_3C_6H_4$) were more deshielded in the coplanar configurations (see Table III).[2,3]

Elimination of HBr. Elimination experiments with both stereoisomeric adducts, involving an excess of triethylamine at room temperature, revealed that not only the cis addition products (2) are capable of undergoing a facile β-trans elimination to give an α-acetylenic sulfone (3) but, surprisingly, also the trans addition products (1), in which H and Br are in a cis relationship,[13] the only difference being, that cis elimination is slower than the trans process.

3

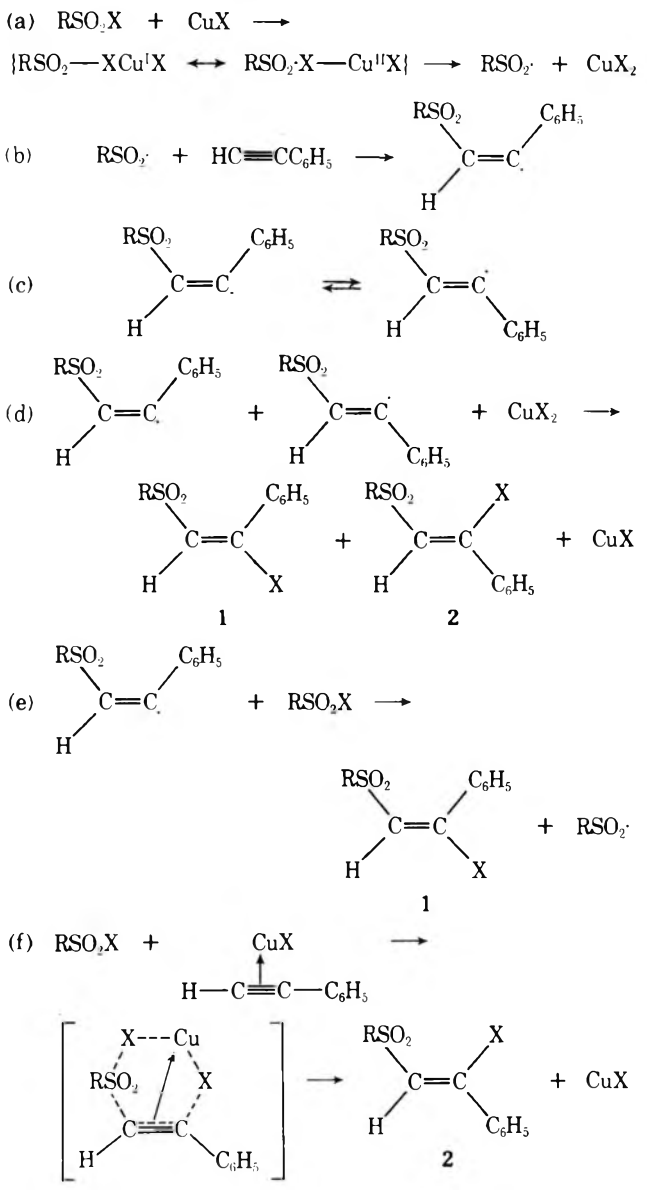
R = CH_3, C_6H_5, p-$CH_3C_6H_4$

It was possible to follow the elimination of HBr from the two isomeric 2-methanesulfonyl-1-bromostyrenes (1 and 2, R = CH_3) by nmr, by the increase of $CH_3SO_2C{\equiv}C-$ singlet at δ 3.31 at the expense of the singlets of the methyl protons of 1 (R = CH_3) at δ 2.71 and of 2 (R = CH_3) at δ 3.21. A benzene solution of 2 (R = CH_3) which was stirred[14] for 20 hr with a large excess of Et_3N at room temperature gave a mixture of 80% of 3 (R = CH_3) and 20% of the unchanged bromo adduct. Under these conditions 1 (R = CH_3) eliminated only 35% HBr.

Dehydrobrominations of 2-benzenesulfonyl-1-bromostyrenes (1 and 2, R = C_6H_5) where somewhat faster, as compared to rates of elimination of HBr from the 2-methanesulfonyl adducts, due to the stronger inductive effect of the 2-benzenesulfonyl group.

As mentioned earlier, Zakharkin and Zhigareva claimed that the thermal addition of benzenesulfonyl bromide to phenylacetylene gave a cis addition product;[9] their structural evidence was based on the fact that the adduct underwent facile elimination of HBr, and hence their conclusion that H and Br had to be in a trans relationship. They apparently did not consider the possibility that a cis elimina-

Scheme I



tion could take place as well. Although the β-trans elimination is the most common elimination process, cis eliminations are also encountered, particularly when the β-hydrogen atom is activated by an electron attracting such as alkyl- or arylsulfonyl group, which favors a two-step E1cb carbanion mechanism.[15]

The reason for the greater ease of cis elimination of HBr from **2**, compared the HCl from its analog, is evidently due to the enhanced leaving ability of the bromide ion from such system.[16] Generally, rates of hydrogen bromide elimination are greater than of hydrogen chloride.[15d,17] The eliminations of hydrogen bromide from the easily accessible adducts of sulfonyl bromide and acetylenes offers a convenient synthesis for α-acetylenic sulfones.

Mechanism for the Addition Reaction. The mechanistic possibilities are summarized in Scheme I. The striking difference between the copper-catalyzed reaction in which mixtures of cis and trans isomers are obtained, and the thermal process which leads exclusively to trans addition products, demonstrates the specific role of the copper catalyst enabling a cis addition process to take place. The possibility of a free-radical reaction including an equilibration step, in which a cis intermediate radical is partially inverted into its trans isomer (step c), leading after halogen transfer (step d), to a mixture of both stereoisomers, was raised previously.[3]

The fact that only the kinetically formed[3] trans addition products are obtained under thermolytic conditions argues strongly against the possibility of an equilibration process (step c) in these reactions. Evidently, the resonance-stabilized cis vinyl radical does not isomerize, and reacts with another sulfonyl halide molecule to give, *via* an halogen chain transfer (step e), the trans addition product. In the presence of cupric halides, which are known as highly reactive halogen donors,[18] the much faster ligand transfer step d supersedes step e;[19] consequently, inversion of the initially formed vinyl radical becomes very improbable, suggesting that the energy barrier for such process (step c) may be fairly high.[20] We suggest, therefore, that the two stereoisomers do not have a common intermediate, and, in general, the formation of the trans addition product, either in the thermal or the copper-catalyzed reaction, is a result of a normal radical chain be it that, in the product forming step, halogen is transferred from the sulfonyl halide or from the copper(II) halide. On the other hand, the cis addition product, which is formed concurrently in the copper-catalyzed reaction, arises presumably from a concerted reaction as depicted in (f). In the stereoselective copper-catalyzed addition of sulfonyl halides to phenylacetylene, the course of the addition could be controlled by polar factors to give preferentially either trans or cis addition products; excess of halide ions, or highly polar solvents, promoted formation of trans addition products, while absence of a supplementary halide salt, or applying a low polarity solvent,[21] resulted a higher ratio of cis addition products.

Excess halide ions give halocuprates with copper(II) ions, which are more soluble in acetonitrile and make for a homogeneous reaction. In the absence of such additives, or in solvents of low polarity, the copper salt is only partly dissolved and we propose that the reaction takes place also on the surface of the undissolved copper catalyst leading to cis addition products; added halide ions may intervene and hinder that process.

In the copper-catalyzed addition of sulfonyl bromides to phenylacetylene, carried out in the absence of excess bromide ions (see Table I, No. 2, 5, and 8), the preference for cis addition products was not as high as in the case of the chloro analogs,[3] apparently due to the competitive thermolytic trans addition.

Experimental Section[22]

Materials. Phenylacetylene obtained from Fluka (puriss) was distilled before use; methanesulfonyl bromide was prepared from methanesulfonyl chloride;[23] benzenesulfonyl bromide and *p*-toluenesulfonyl bromide were prepared from the corresponding arylsulfinic acid sodium salts,[24] or from the corresponding arylsulfonylhydrazides;[4d] anhydrous cupric bromide (Baker Chemical Co., reagent grade) and lithium bromide (B.D.H., reagent grade) were dried at 110° to constant weight; acetonitrile from Fluka (puriss) was dried over P_2O_5; Kieselgel 70–325 mesh was obtained from Merck.

(*E,Z*)-2-Benzenesulfonyl-1-bromostyrenes (1 and 2, R = C_6H_5). A mixture of 2.21 g (10 mmol) of benzenesulfonyl bromide, 1.12 g (11 mmol) of phenylacetylene, 45 mg (2 mmol) of anhydrous cupric bromide, and 52 mg (6 mmol) of anhydrous lithium bromide in 2 g of acetonitrile was introduced into a Carius tube, cooled in liquid air, degassed (three times) at 0.1 mm, sealed, and heated for 4 hr at 100°. After contraction was stopped the tube was cooled in liquid air and then opened. The semisolid reaction mixture was dissolved in methylene chloride, transferred to a separatory funnel, and washed with water and an aqueous solution of disodium ethylenediaminetetraacetate until free from copper, and the organic layer was dried (Na_2SO_4). The solvent was evaporated and the crude reaction mixture (3.2 g) was dissolved in a minimum amount of methylene chloride (3–5 ml) and chromatographed over 70 g of Kieselgel. Elution with ether–*n*-hexane (1:6) gave 2.45 g

(76%) of 1 (R = C_6H_5): mp 82° (methanol); ir 6.19, 6.28, 6.72, 6.92, 7.17, 7.58, 7.78, 8.80, 9.24, 9.75, 10.0, 10.85, 11.4, and 12.4 μ.

Anal. Calcd for $C_{14}H_{11}BrO_2S$: C, 52.02; H, 3.43; Br, 24.72; S, 9.92. Found: C, 52.18; H, 3.55; Br, 24.50; S, 9.87.

Further elution with ether–*n*-hexane (1:4) of the same chromatogram afforded 0.45 g (14%) of 2 (R = C_6H_5): mp 88° (methanol); ir 6.28, 6.37, 6.72, 6.92, 7.17, 7.58, 7.78, 8.08, 8.50, 8.72, 9.22, 10.0, 10.05, 10.35, 10.85, 11.1, 11.3, and 12.3 μ.

Anal. Calcd for $C_{14}H_{11}BrO_2S$: C, 52.02; H, 3.43; Br, 24.72; S, 9.92. Found: C, 52.18; H, 3.55; Br, 24.50; S, 9.87.

(*E,Z*)-2-Methanesulfonyl-1-bromostyrenes (1 and 2, R = CH_3). The addition reaction and the work-up procedure were carried out as described for benzenesulfonyl bromide using 1.59 g (10 mmol) of methanesulfonyl bromide. Elution with ether–*n*-hexane (1:4) gave 2.07 g (79%) of 1 (R = CH_3): mp 60.5° (ethanol); ir 6.19, 6..29, 6.72, 6.92, 7.16, 7.58, 7.75, 8.82, 9.4, 10.5, 11.3, 11.5, and 12.4 μ.

Anal. Calcd for $C_9H_9BrO_2S$: C, 41.39; H, 3.47; Br, 30.60; S, 12.28. Found: C, 41.35; H, 3.54; Br, 30.80; S, 12.13.

Further elution with ether–*n*-hexane (1:3) of the same chromatogram afforded 0.28 g (11%) of 2 (R = CH_3): mp 76° (ethanol); ir 6.29, 6.36, 6.72, 6.92, 7.16, 7.58, 8.82, 9.4, 10.5, 11.15, and 12.3 μ.

Anal. Calcd for $C_9H_9BrO_2S$: C, 41.39; H, 3.47; Br, 30.60; S, 12.28. Found, C 41.20; H, 3.50; Br, 30.89; S, 12.09.

(*E,Z*)-2-*p*-Toluenesulfonyl-1-bromostyrenes (1 and 2, R = *p*-$CH_3C_6H_4$). The addition reaction and the work-up procedure were carried out as described for benzenesulfonyl bromide using 2.35 g (10 mmol) of *p*-toluenesulfonyl bromide. Elution with ether–*n*-hexane (1:6) gave 2.6 g (77%) of 1 (R = *p*-$CH_3C_6H_4$): mp 103–104° (methanol); ir 6.19, 6.28, 6.72, 6.92, 7.17, 7.55, 7.65, 7.75, 8.70, 9.25, 9.65, 9.85, 10.0, 10.85, 11.2, 11.3, and 12.4 μ.

Anal. Calcd for $C_{15}H_{13}BrO_2S$: C, 53.42; H, 3.89; Br, 23.70; S, 9.51. Found: C, 53.20; H, 3.79; Br, 23.94; S, 9.56.

Further elution with ether–*n*-hexane (1:3) of the same chromatogram afforded 0.54 g (16%) of 2 (R = *p*-$CH_3C_6H_4$): mp 108–109° (methanol); ir 6.26, 6.30, 6.37, 6.72, 6.92, 7.16, 7.55, 7.65, 7.71, 8.68, 9.20, 9.62, 9.8, 10.0 10.85, 11.15, 11.3, and 12.4 μ.

Anal. Calcd for $C_{15}H_{13}BrO_2S$: C, 53.42; H, 3.89; Br, 23.70, S, 9.51. Found: C, 53.60; H, 3.84; Br, 23.99; S, 9.62.

Eliminations of HBr from 1 and 2 (R = CH_3, C_6H_5, *p*-$CH_3C_6H_4$). Eliminations were carried out by stirring[14] a solution of the adduct (2 mmol) in benzene (2 ml) and triethylamine (2 ml) at room temperature; dehydrobromination was noted by precipitation of the amine hydrobromide and reaction was followed by nmr [disappearance of vinylic proton, or shift of the methyl singlet (1 and 2 → 3, R = CH_3, *p*-$CH_3C_6H_4$)]. The acetylenic sulfones were obtained after removal of the hydrobromide by filtration, evaporation of the volatiles, and crystallization from methanol. Yields were almost quantitative. Reaction times (hr) required for complete elimination of HBr from 1 and 2 under these conditions were

	CH_3	C_6H_5	*p*-$CH_3C_6H_4$
1	72	16	36
2	30	12	24

1-Phenyl-2-metanesulfonylethyne (3, R = CH_3). This compound was prepared either from 1 (R = CH_3) or 2 (R = CH_3) by the above described procedure: mp 68–69° (lit.[5,25] 63–64°, 68.5–69.5°); ir 4.59 (–C≡C–), 7.65, and 8.60 μ (–SO_2–); nmr δ 3.31 (S, 3 H, CH_3), 7.35–7.65 (m, 5 H, aromatic).

Anal. Calcd for $C_9H_8O_2S$: C, 59.98; H, 4.47; S, 17.79. Found: C, 59.92; H, 4.53; S, 17.85.

1-Phenyl-2-benzenesulfonylethyne (3, R = C_6H_5). This compound was prepared either from 1 (R = C_6H_5) or 2 (R = C_6H_5) by the above described procedure: mp 74.5° (lit.[26] 73–74°) was identical with that of an authentic sample.[2]

1-Phenyl-2-*p*-toluenesulfonylethyne (3, R = *p*-$CH_3C_6H_4$). This compound was prepared either from 1 (R = *p*-$CH_3C_6H_4$) or 2 (R = *p*-$CH_3C_6H_4$) by the above described procedure: mp 82–83° (lit.[5,27] 83–84°, 80–81°); ir 4.59 (–C≡C–), 7.65, and 8.60 μ (–SO_2–); nmr δ 2.43 (s, 3 H, CH_3), 7.20–7.70 (m, 7 H, aromatic), 7.98 (d, 2 H, aromatic, J = 8.5 Hz).

Anal. Calcd for $C_{15}H_{12}O_2S$: C, 44.09; H, 8.81; S, 23.54. Found: C, 44.16; H, 8.78; S, 23.60.

Registry No.—1 (R = C_6H_5), 52920-43-1; 1 (R = CH_3), 52920-44-2; 1 (R = *p*-$CH_3C_6H_4$), 52920-45-3; 2 (R = C_6H_5), 52920-46-4; 2 (R = CH_3), 52920-47-5; 2 (R = *p*-$CH_3C_6H_4$), 52920-48-6; 3 (R = CH_3), 24378-05-0; 3 (R = C_6H_5), 5324-64-1; 3 (R = *p*-$CH_3C_6H_4$), 28995-88-2; phenylacetylene, 536-74-3; benzenesulfonyl bromide, 2297-65-6; methanesulfonyl bromide, 41138-92-5; *p*-toluenesulfonyl bromide, 1950-69-2.

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(11) Usually a slight excess of phenylacetylene is used because of a minute amount of the acetylene undergoes bromination. Same results were obtained when a large excess of sulfonylbromide was used; prolonged heating did not lead to the addition of a second molecule of sulfonyl bromide to the ethylenic bond of the 1:1 adduct.
(12) In acetonitrile, reactions were generally cleaner but a bit slower than without any solvent.
(13) The chloro analogs of 1 do not undergo eliminations, and are recovered unchanged even after prolonged heating with a tertiary amine.[2]
(14) Without stirring the dehydrobromination is much slower.
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Oxidation of Olefins by Palladium(II). VII. Comparison of Palladium(II) Chloride with Other Noble Metal Salts in the Copper(II) Chloride Promoted Oxidation in Acetic Acid[1]

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Studies of the $CuCl_2$-promoted oxidation of olefins to chloro- or diacetates by $PdCl_2$ in acetic acid have been extended to other noble metal chlorides. $PtCl_2$ was found to be more effective than $PdCl_2$ in the oxidation of cyclohexene to saturated esters, whereas $RhCl_3$ and $IrCl_3$ were less active than $PdCl_2$. $PtCl_2$ gave almost exclusively 1,2-disubstituted cyclohexanes, while $PdCl_2$ and $RhCl_3$ gave appreciable amounts of 1,3 and 1,4 isomers along with the 1,2 isomers. The ratios of chloro- to diacetates, as well as the distribution of geometric isomers, was also quite different for the four noble metal salts which gave saturated esters. $PtCl_2$ also oxidized 1-butene exclusively to 1,2 isomers and *cis*- and *trans*-2-butene exclusively to 2,3 isomers. The product distributions were again quite different from those obtained with $PdCl_2$ under the same reaction conditions in regard to positional isomerism, geometric isomerism, and ratios of chloro- to diacetates. The results of this study provide evidence against a mechanism involving alkyl transfer from noble metal to Cu(II).

The oxidation of olefins to saturated ester or ether products by Pd(II) salts plus other oxidants, such as $CuCl_2$, $Tl(OAc)_3$, $Pb(OAc)_4$, $AuCl_3$, NO_3^-, KCr_2O_7, Br_2, or Cl_2 has now been the subject of several studies.[1,3-13] The most reasonable mechanism consistent with other palladium chemistry appears to be capture of an oxypalladation intermediate by the oxidant to give the saturated products instead of the unsaturated products found in the absence of oxidant. For ethylene in acetic acid, the reaction scheme would be given by equation 1 (X = OAc or Cl)

$$C_2H_4 + Pd(II) + OAc^- \longrightarrow Pd(II)-CH_2CH_2OAc \xrightarrow{-HPd(II)} CH_2=CHOAc \quad (1)$$

$$Pd(II)-CH_2CH_2OAc \xrightarrow[X^-]{\text{oxidant}} Pd(II) + XCH_2CH_2OAc$$

When higher olefins are used, products are formed[5,9] which must have resulted from movement of Pd(II) down the carbon chain before reacting with oxidant. Thus 2-butene gives 1,3- as well as 1,2-disubstituted butenes when oxidized by the $PdCl_2$–$CuCl_2$ system in acetic acid. The

$$CH_3CH=CHCH_3 + Pd(II) + OAc^- \longrightarrow CH_3CH(Pd(II))-CHCH_3(OAc) \quad (2)$$

$$Pd(II) + XCH_2CH_2CHCH_3(OAc) \xleftarrow[X^-]{CuCl_2} Pd(II)-CH_2CH_2CHCH_3(OAc)$$

movement down the chain almost certainly occurs by Pd(II) hydride eliminations and readditions.

The reason for the change in product distribution in the presence of oxidant is most likely related to the nature of decomposition of Pd(II) alkyls. Since monomeric Pd(0) is an unstable species, the Pd(II)–carbon bond does not break heterolytically to give Pd(0) and a carbonium ion. Rather Pd(II) hydride is eliminated to give olefin. The oxidant is believed to facilitate the heterolytic decomposition of the Pd(II)–carbon bond by avoiding the necessity of forming Pd(0), thus giving substitution rather than elimination products.

The exact means whereby the oxidant accomplishes this change in product distribution is not certain and may differ for different oxidants. Possibilities are (1) transfer of alkyl to oxidant followed by decomposition; (2) oxidation transfer of alkyl to oxidant followed by decomposition; (2) oxidation of Pd(II) to Pd(IV) followed by decomposition; and (3) removal of electrons from the Pd(II) as the Pd(II)–carbon bond is being broken.

$$\text{oxidant}\cdots Pd(II)-CH_2CH_2OAc \longrightarrow \text{reduced oxidant} + Pd(II) + XCH_2CH_2OAc \quad (3)$$

(X^- on Pd(II))

One possible means of distinguishing between the first and the other two possibilities is the use of other noble metal salts as replacements for Pd(II). If complete transfer of the organic moiety to oxidant occurs, the product distribution for a given positional isomer should be independent of the noble metal used.

The purpose of this study is to determine if other noble metal salts can be used in place of $PdCl_2$ in the $CuCl_2$-promoted reaction and to see if the product distributions vary from one noble metal to another.

Results

The activity of the other noble metal salts in the $CuCl_2$-promoted oxidation of olefins was first tested using cyclohexene as substrate. Reaction times of only 1 hr at 75° were used to ensure products were primary oxidation products. Results are given in Table I. The formation of saturated products is an indication of activity of the noble metal salt. By this criterion $RuCl_3$[14] and $OsCl_3$ are inactive, while $IrCl_3$ and $RhCl_3$ have low activity. $PtCl_2$ was more reactive than $PdCl_2$ in producing saturated ester.

$PtCl_2$ and $RhCl_3$ were chosen for further study. In Table II are given the product distributions for cyclohexene oxidation under two sets of reaction conditions. Longer reaction times were used to increase conversions, thus enabling more accurate product distribution determinations. Once again $PtCl_2$ is most active for production of saturated esters, while $PdCl_2$ is most active for production of unsaturated esters. $PtCl_2$ also gives the simplest product distributions. At low chloride concentrations, only one unsaturated and two of the three possible 1,2 isomers are formed. No 1,3 or 1,4 isomers were detected. $PdCl_2$ and $RhCl_3$ gave 1,2, 1,3, and 1,4 isomers with the product distributions most complicated for $PdCl_2$. At high chloride, the same general trends are observed except that $PtCl_2$ does now give small amounts of other positional isomers as well as *cis*-1,2-chloroacetate. The product distributions with $PdCl_2$ and $RhCl_3$ also display more positional isomerization. With both, the

Table I
Test of Various Noble Metals for Oxidation of Cyclohexene with Cupric Chloride at 75°[a]

	Concentration, 10^3 M^b					
Products	$PdCl_2$	$PtCl_2$	$RhCl_3$	$RuCl_3$	$IrCl_3$	$OsCl_3$
Unsaturated Esters						
2-Cyclohexen-1-yl acetate	6.0	6.3	4.7	0.73	0.61	4.0
3-Cyclohexen-1-yl acetate	0.5	ND	1.6	ND	ND	1.4
1,2 Isomers						
trans-Chloroacetate	1.3	4.8	0.12	ND	0.18	ND
cis-Chloroacetate	0.9	ND	ND	ND	ND	ND
cis-Diacetate	0.9	11.8	0.25	ND	0.25	ND
Other Isomers						
trans-1,3- and -1,4-chloroacetate	0.8	ND	ND	ND	ND	ND
cis-1,4-Chloroacetate	0.06	ND	ND	ND	ND	ND
cis-1,3- and -1,4-diacetate	0.16	ND	ND	ND	ND	ND
trans-1,3-Diacetate	ND	ND	0.1	ND	ND	ND

[a] All contain 0.5 mol of cyclohexene, 1.0 mol of cupric chloride, 0.01 mol of metal salt, and 1.0 mol of lithium acetate per liter of acetic acid and were run for 2 hr. Soluble [Cu(II)] = 0.75 *M* in this system. [b] 1-Cyclohexen-1-yl acetate and *trans*-1,2- or -1,4-diacetate were not detected in any of the runs; *trans*-1,3- and -1,4-chloroacetates as well as *cis*-1,3- and -1,4-diacetate were not separated by gas–liquid chromatography (glc). ND means not detected. Level of detection is 0.1×10^{-3} *M*.

Table II
Product Distributions for the Oxidation of Cyclohexene with Three Noble Metal Salts at 75°

	Concentration, 10^3 M^c					
	Low chloride (23 hr)[a]			High chloride (49 hr)[b]		
Products	$PdCl_2$	$PtCl_2$	$RhCl_3$	$PdCl_2$	$PtCl_2$	$RhCl_3$
Unsaturated Esters						
2-Cyclohexen-1-yl acetate	86	21	12	5.2	5.4	3.7
3-Cyclohexen-1-yl acetate	71	ND	17	18	0.8	24
1,2 Isomers						
trans-Chloroacetate	4.4	43	0.5	7.5	35	1.3
cis-Chloroacetate	3.2	ND	ND	11	5.9	0.5
cis-Diacetate	5.3	32	2.2	7.7	63	4.0
Other Isomers						
trans-1,3- and -1,4-chloroacetate	11	ND	ND	9.8	ND	0.7
cis-1,4-Chloroacetate	0.6	ND	ND	0.8	ND	1.9
cis-1,3- and -1,4-diacetate	7.8	ND	0.4	1.5	14	1.7
trans-1,3-Diacetate	1.2	ND	1.1	0.9	3.1	ND

[a] Reaction mixture identical with that in Table I. [b] Same as low chloride except it also contains 2.0 mol of lithium chloride per liter of acetic acid. This reaction mixture is homogeneous. [c] Same comment as *b* of Table I.

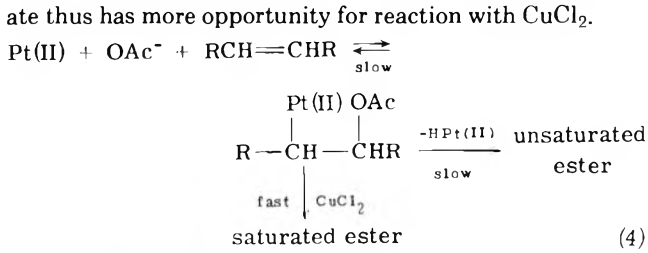
3-cyclohexen-1-yl acetate becomes the main unsaturated product.

Next the oxidation of the butenes by $PdCl_2$ and $PtCl_2$ was studied. Product distributions for $PdCl_2$ under one set of reaction conditions have been reported.[7] Product distributions for oxidation of *cis*- and *trans*-2-butene under several reaction conditions are given in Table III. The data are presented in terms of ratios of positional and geometric isomers as well as ratios of chloro- to diacetate. These data indicate $PdCl_2$ gives considerable positional isomerization. The ratios of other products do not appear to follow any simple pattern.

The product distributions obtained by oxidation of the butenes by $PtCl_2$ plus $CuCl_2$ for one set of reaction conditions is given in Table IV. No positional isomerization has occurred but *cis*- and *trans*-2-butene gives mixtures of all possible 2,3 products. Particularly interesting is the fact that the *threo*-chloroacetate is the main product with both olefin isomers.

Discussion

Probably the most unexpected result of this work is the high reactivity of $PtCl_2$ in the $CuCl_2$-promoted reaction since, in general, Pt(II) is less labile than Pd(II). This higher reactivity can probably best be rationalized in terms of a higher steady state concentration of the acetoxymetalation adduct from Pt(II) as compared with the corresponding intermediate from Pd(II). Thus deacetoxymetalation as well as decomposition by Pt(II) hydride elimination would be much slower for Pt(II) than for Pd(II) and the intermediate thus has more opportunity for reaction with $CuCl_2$.



(4)

The lower yields of unsaturated esters and positional isomers with Pt(II) as compared with the other noble metal salts are understandable in terms of the stability of Pt(II) alkyls to decomposition by Pt(II) hydride elimination. As shown in eq 5, both of these products require Pt(II) hydride elimination (X = Cl or OAc).

trans-$Pt(C_2H_5)Cl(PEt_3)_3$ decomposes to *trans*-$PtHCl(PEt_3)_2$ and ethylene only at 180°[15] while Pd(II) alkyls with β hydrogen decompose rapidly at room temperature.[16] The position isomerization of the saturated esters requires readdition of Pt(II) hydride which also does not occur very readily.[15]

The product distributions with the various noble metal salts also provide evidence against one of the possible mechanisms suggested in the introductory paragraph. If

Table III
Effect of Reaction Conditions on Product Distributions for Oxidation of *cis*- and *trans*-2-Butene by $PdCl_2$ Plus $CuCl_2$

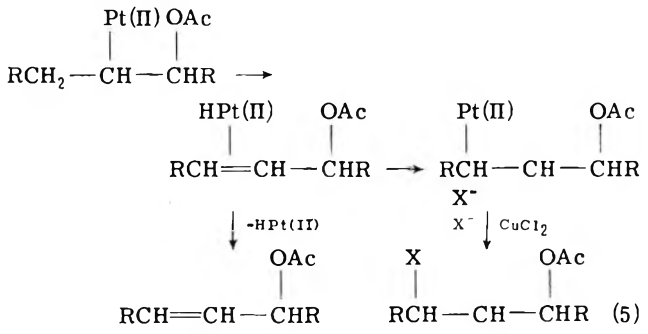
Reaction[a] mixture	Temp, °C	[1,3 isomer]/[2,3 isomer]		[Diacetate]/[chloroacetate] 2,3 isomer		1,3 isomer		Chloroacetate [erythro]/[threo]		Diacetate [meso]/[dl]	
		Cis	Trans	Cis	Trans	Cis	Trans	Cis	Trans	Cis	Trans
Very low Cl	25	1.6	0.95	4.3	0.81	19	1.4	2.2	4.7	11	0.09
Low Cl	25	0.8	0.22	0.59	0.65	0.63	0.60	0.2	3.5	>10	0.15
High Cl	25	0.11	0.05	0.34	0.44	*b*	1.4	12	0.71	>10	0.15
Very low Cl	100	3.2	2.1	0.21	0.94	0.11	2.7	0.8	2.4	0.65	0.40
Low Cl	100	2.2	0.65	0.51	0.39	0.20	0.22	0.43	2.2	3.6	0.52
High Cl	100	0.17	1.0	0.61	0.33	0.32	0.93	0.75	0.86	8.3	0.22

[a] Low Cl and high Cl corresponds to reaction mixtures of Table II. Very low Cl is same as low Cl except sodium acetate is used in place of lithium acetate. At 25°, atmospheric olefin was used, while at 100°, the pressure was the maximum at this temperature. At 25°, the reaction time was 8 hr, while at 100°, it was 1 hr. [b] No 1,3 isomer was detected.

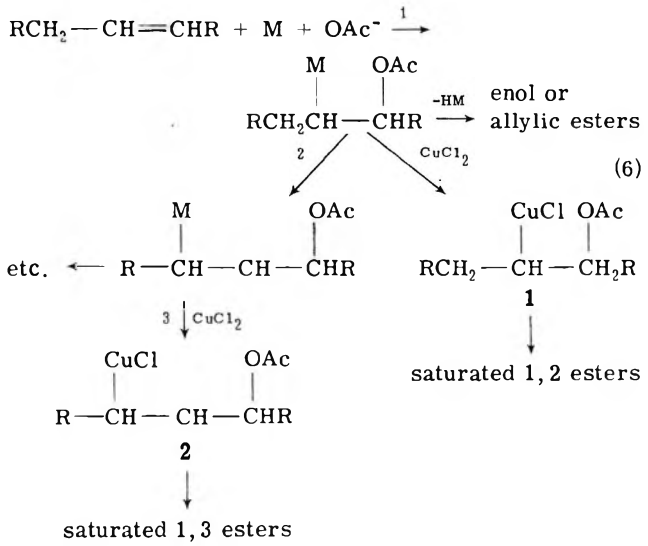
Table IV
Product Distributions from the Oxidation of the Butenes by $PtCl_2$ Plus $CuCl_2$ at 100°[a]

Products	Concentration, 10^3 M[b] *cis*-2-Butene	*trans*-2-Butene	1-Butene
2,3 Isomers			
erythro-Chloroacetate	0.5	1.6	ND
threo-Chloroacetate	15.0	7.8	ND
meso-Diacetate	1.2	1.1	ND
dl-Diacetate	1.1	0.82	ND
1,2 Isomers			
1-Chloro-2-acetoxybutane	ND	ND	20.3
2-Chloro-1-acetoxybutane	ND	ND	4.5
1,2 Diacetate	ND	ND	1.7

[a] Reaction mixture identical with low chloride in Table III. Run for 1 hr at maximum olefin pressure. [b] ND means not detected ($<0.1 \times 10^{-3}$ M).



the mechanism involves transfer of alkyl to $CuCl_2$ the general scheme would be given by eq 6 (R = H, CH_3, $-CH_2-$; M = Pd(II), Pt(II), Rh(III) etc.).



Now the ratio of 1 and 2 and thus the degree of positional isomerization will depend on M. However, for each positional isomer, the stereochemistry of the products will be independent of M since they will depend on the mode of decomposition of the copper(II) alkyls, **1** and **2**. The results with cyclohexene shown in Tables I and II definitely indicate that the product distributions for the 1,2 positional isomers under one set of reaction conditions do depend on the noble metal salt used. As an example, Pd(II) consistently gives more *cis*-1,2-chloroacetate. In addition the ratio of *trans*-chloroacetate to *cis*-diacetate varies from greater than one for $PdCl_2$ to *ca.* 0.75 for $IrCl_3$ to *ca.* 0.5 for $RhCl_3$ to *ca.* 0.4 for $PtCl_2$. Similar trends are found in Table II.

The results for *cis*- and *trans*-butene also show that product distributions depend on identity of the noble metal salt. The low chloride run in Table III compares with the reaction conditions of Table IV. The following comparisons can be made.

(1) Diacetate:Chloroacetate Ratio. For Pd(II) (2,3 isomers) it is 0.51 for the *cis*-2-butene and 0.39 for the trans isomer. The corresponding ratios for Pt(II) are 0.15 and 0.2.

(2) Erythro:Threo Ratio. For Pd(II) the cis ratio is 0.43 and the trans is 2.2. The corresponding ratios for Pt(II) are 0.033 and 0.20.

(3) Meso Diacetate:*dl* Diacetate Ratio. For Pd(II) the cis ratio is 3.6 while the trans is 0.52. The corresponding ratios for Pt(II) are 0.11 and 1.35.

All these ratios are considerably different for Pd(II) and Pt(II).

One question that was not considered in the above discussion concerns the stereochemistry of the intermediate **2**. Depending on the stereochemistries of steps 1 and 2 this intermediate could be cis or trans with cyclohexene and threo or erythro with *cis*- or *trans*-2-butene. The two different geometric isomers might well give different modes of decomposition of **2**. The tacit assumption is that all the noble metal salts would be expected to have similar chemistry and thus the same stereochemistry for steps 1 and 2. For $PdCl_2$, step 1 has been demonstrated to have trans stereochemistry.[11]

Of course there is the possibility that, for instance, $PdCl_2$ and $PtCl_2$ may have different stereochemistries for either of the two steps. However, if that were the case, the **2** isomer from *cis*-2-butene and $PdCl_2$ would be identical with the **2** isomer from *trans*-2-butene and $PtCl_2$. However, the cis or trans isomer ratios for one metal salt do not match with the respective trans or cis isomer ratios for the other metal salt. Thus, even if the stereochemistries of steps 1 and 2 were different for $PdCl_2$ and $PtCl_2$, the arguments against the mechanism represented by this scheme would still be valid.

The product distribution for the oxidation of cyclohexene by $PdCl_2$ plus $CuCl_2$ is similar to those previously reported and consistent with a scheme involving trans acetoxypalladation followed by trans elimination of Pd(II) by acetate and cis or trans elimination of Pd(II) by chloride. The other positional isomers are formed by movement of Pd(II) around the ring in the intermediate acetoxypalladation adduct by Pd(II) hydride eliminations and readditions. In the 1,3 and 1,4 isomers the diacetates are always cis and the chloroacetates predominantly trans.

The scheme for the other noble metal salts is probably very similar. However, they give much smaller amounts of *cis*-1,2-chloroacetate than does $PdCl_2$, indicating cis elimination of noble metal by chloride is much less favored than for Pd(II).

The noble metal salts also differ considerably in their ability to move about the cyclohexane ring. Thus as can be seen from Table I, $RhCl_3$ and $OsCl_3$ gave more 3-cyclohexen-1-yl acetate than $PdCl_2$, while the other three gave none of this isomer. In this light, the much higher ratios of the 3 isomer at longer reaction times (Table II) suggests that the noble metal is catalyzing the isomerization of the 2 isomer to the 3 isomer.

The product distributions in Table III defy any simple explanation but follow some trends. Thus the amount of positional isomerization (1,3/1,2 isomer) increases with temperature and generally decreases with increasing soluble chloride concentration. As might be expected, the diacetate:chloroacetate ratio decreases with increasing soluble chloride at 25°, but, at 100°, the trends are more complicated. The ratio increases with increasing soluble chloride, for *trans*-2-butene, but increases for the cis isomer.

The meso:*dl* ratios at 25° are consistent with the scheme found for cyclohexene; trans acetoxypalladation followed by trans elimination of Pd(II). At 100°, the trends become more complicated, with the ratios differing considerably at differing soluble chloride concentrations.

Since the cyclohexene work indicated that Pd(II) can be displaced in both cis and trans fashion by chloride, the erythro:threo ratios for the 2,3-chloroacetates might be expected to be quite complicated. As can be seen from Table III, they follow no simple trends. The erythro for the *cis*-2-butene corresponds to trans addition—trans elimination (*cis*-1,2-chloroacetate in the cyclohexene system), while the threo isomer corresponds to the same series of steps for *trans*-2-butene. The fact that the trends in this case are so complicated and so different for the *cis*- and *trans*-2-butene indicates that subtle factors, such as conformational energies in the intermediate acetoxypalladation adduct, may be important. However, the present results do not permit a detailed discussion of the possible factors.

Finally one interesting aspect of the product distributions obtained from the 2-butenes is the fact that both the cis and trans isomers gave predominantly the *threo*-chloroacetate. This result could have synthetic utility, since a mixture of both isomers would give the same chloroacetate. The reason why the threo isomer is preferred for both olefins is not obvious and speculation as to possible reasons does not seem warranted.

Experimental Section

Materials. Aldrich cyclohexene was distilled and stored under N_2. The butenes were Phillips Petroleum Co. pure grade. $PdCl_2$ was purchased from Engelhardt Industries. The other noble salts were purchased from Alfa. All other chemicals were reagent grade. The preparation of dry acetic acid has been described.[17]

Experimental Procedure. The reaction procedure as well as workup of the reaction mixture has been described for both cyclohexene[11] and the butenes.[7] Product analyses were carried out by vapor phase chromatography with a 15-ft 10% UCON 75h column on Gas-Chrom Z. For the cyclohexene oxidation products, the column was programmed from 130 to 200° at 2.4°/min, while for the butenes it was programmed from 110 to 170° at 2.4°/min. The preparation of the standards the cyclohexene oxidation has been described,[11] as has the preparation of most of the standards for the butene oxidation.[7] The *meso*- and *dl*-2,3-diacetates were prepared by the acetylation of the corresponding glycols which were kindly supplied by Dr. E. J. Vandenberg of Hercules. The *threo*- and *erythro*-2,3-chloro alcohols were prepared by the reaction of *cis*- and *trans*-2,3-epoxybutane with HCl, respectively.[18] They were acetylated to give the chloroacetates.

Acknowledgments. The author gratefully acknowledges the technical assistance of Mr. F. Kriss.

Registry No.—$CuCl_2$, 7447-39-4; $PdCl_2$, 7647-10-1; $PtCl_2$, 10025-65-7; $RhCl_3$, 10049-07-7; $RuCl_3$, 10049-08-8; $IrCl_3$, 10025-83-9; $OsCl_3$, 13444-93-4; cyclohexene, 110-83-8; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; 1-butene, 106-98-9.

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Reactions of Silver Perchlorate and of Silver Triflate with Alkyl Iodides. Solvent Inhibition of Isomerization[1]

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Primary alkyl iodides reacted with silver perchlorate and with silver triflate in pentane, carbon tetrachloride, or 1,1,2-trichlorotrifluoroethane to give mixtures of the primary and secondary perchlorates and triflates, respectively, with secondary isomers predominating. In benzene, only the unrearranged products were obtained. An excess of alkyl iodide and, to a lesser extent, methylene chloride also inhibited isomerization. Isopropyl iodide and allyl iodide, as well as primary iodides, were converted to the corresponding perchlorates and triflates in high yield. Inhibition of rearrangement is rationalized on the basis of lessened reactivity of complexed silver ions.

Substitution reactions of alkyl halides with silver salts are widely used synthetic methods. With poorly nucleophilic anions, however, the utility has been limited because of isomerization. The reaction of silver perchlorate with primary alkyl iodides in pentane gave mainly secondary perchlorates,[2] and the reaction of silver trifluoromethanesulfonate with propyl iodide under the same conditions also was reported to give mainly isopropyl triflate.[3] No evidence of rearrangement was reported in reactions of alkyl halides with silver salts of more nucleophilic anions, such as nitrite,[4] nitrate,[5] and toluenesulfonate.[6] The present paper deals with the effects of solvents on the reactions of silver perchlorate and silver triflate with alkyl iodides and describes selective synthetic procedures for simple primary perchlorates and triflates.

The initial studies were carried out using propyl iodide, since only one secondary substitution product is possible, and the isomeric perchlorates[2] and triflates[3,7] are readily distinguished by nmr. Propyl iodide reacted with a suspension of anhydrous silver perchlorate in pentane, carbon tetrachloride, or 1,1,2-trichlorotrifluoroethane to give a quantitative yield of perchlorates, consisting of 60% isopropyl perchlorate and 40% propyl perchlorate. The product ratio in this heterogeneous reaction was affected by variables such as the particle size of the silver perchlorate and the rate of stirring. variations of up to 10% in yields of the components were observed, but the total yield remained essentially quantitative.

When this reaction was carried out in benzene, in which silver perchlorate is soluble, a 91% yield of propyl perchlorate was obtained. No isopropyl perchlorate was detected by nmr or by glpc of the displacement products with lithium bromide, and no benzene alkylation products were detected. When such a large excess of silver perchlorate was used that the salt was mainly out of solution, the same results were obtained, showing that the results were not due simply to homogeneous and heterogeneous reactions. The use of mixtures of carbon tetrachloride and benzene gave intermediate results. Thus, a solvent consisting of 33% benzene and 67% carbon tetrachloride gave an equal mixture of propyl perchlorate and isopropyl perchlorate. A solvent consisting of 67% benzene and 33% carbon tetrachloride gave a product containing 15% isopropyl perchlorate and 85% propyl perchlorate. Methylene chloride as a reaction solvent also gave results intermediate between those for benzene and carbon tetrachloride and the product consisted of 62% propyl perchlorate and 38% isopropyl perchlorate. The use of an excess of propyl iodide, with carbon tetrachloride as the reaction solvent, was also found to reduce the amount of rearrangement. Twice the theoretical amount of propyl iodide gave 41% rearranged product, and four times the theoretical amount of propyl iodide gave only 23% rearrangement.

Reactions of silver triflate with propyl iodide gave results similar to those of silver perchlorate. In carbon tetrachloride, pentane, or 1,1,2-trichlorotrifluoroethane, the product consisted of 34% propyl triflate and 66% isopropyl triflate. Methylene chloride gave 59% propyl triflate and 41% isopropyl triflate. Benzene gave completely unrearranged propyl triflate. Also, as in the perchlorate reactions, diluted benzene gave intermediate results. Thus, 33% benzene in 1,1,2-trichlorotrifluoroethane gave 57% rearrangement, 50% benzene gave 49% rearrangement, and 67% benzene gave 23% rearrangement. An excess of propyl iodide as solvent gave only unrearranged propyl triflate.

For preparative purposes, carbon tetrachloride and similar solvents are preferred for substrates that do not isomerize readily. The reactions are more rapid than those in benzene solution, and the products are observed conveniently by nmr. Benzene is the solvent of choice for substrates prone to rearrangement. Preparations of organic perchlorates and triflates from silver perchlorate and silver triflate are shown in Tables I and II, respectively. Spectral properties of the perchlorates were identical with those of the compounds obtained from the corresponding alcohols and dichlorine heptoxide.[2] Triflates were compared likewise with authentic samples.[7] Pentyl triflate, hexyl triflate, and decyl triflate were isolated, and the latter two, which are new compounds, were analyzed. Propyl triflate was also prepared independently from propanol and triflic anhydride.

Hexyl iodide and silver perchlorate in carbon tetrachlo-

Table I
Reactions of Alkyl Iodides with Silver Perchlorate

Starting material	Registry no.	Product	Solvent	Yield, %
CH_3I	74-88-4	CH_3OClO_3	CCl_4	81
CH_3CH_2I	75-03-6	$CH_3CH_2OClO_3$	CCl_4	99
$(CH_3)_2CHI$	75-30-9	$(CH_3)_2CHOClO_3$	CCl_4	98
$CH_2{=}CHCH_2I$	556-56-9	$CH_2{=}CHCH_2OClO_3$	CCl_4	96
$CH_3CH_2CH_2I$	107-08-4	$CH_3CH_2CH_2OClO_3$	C_6H_6	91
$CH_3(CH_2)_3CH_2I$	628-17-1	$CH_3(CH_2)_3CH_2OClO_3$	C_6H_6	86
$CH_3(CH_2)_4CH_2I$	638-45-9	$CH_3(CH_2)_4CH_2OClO_3$	C_6H_6	87

Table II
Reactions of Alkyl Iodides with Silver Triflate

Starting material	Product	Solvent	Yield, %
CH_3I	$CH_3OSO_2CF_3$	CCl_4	85
CH_3CH_2I	$CH_3CH_2OSO_2CF_3$	CCl_4	98
$(CH_3)_2CHI$	$(CH_3)_2CHOSO_2CF_3$	CCl_4	97
$CH_2{=}CHCH_2I$	$CH_2{=}CH_2CHOSO_2CF_3$	CCl_4	95
$CH_3CH_2CH_2I$	$CH_3CH_2CH_2OSO_2CF_3$	C_6H_6	92
$CH_3(CH_2)_3CH_2I$	$CH_3(CH_2)_3CH_2OSO_2CF_3$	C_6H_6	82
$CH_3(CH_2)_4CH_2I$	$CH_3(CH_2)_4CH_2OSO_2CF_3$	C_6H_6	91
$CH_3(CH_2)_8CH_2I$	$CH_3(CH_2)_8CH_2OSO_2CF_3$	C_6H_6	93

ride gave mainly secondary perchlorates, and both 2-hexyl perchlorate and 3-hexyl perchlorate were identified as the corresponding bromides following reaction with lithium bromide.

$$CH_3(CH_2)_5I + AgClO_4 \xrightarrow{CCl_4} CH_3(CH_2)_5OClO_3 + CH_3(CH_2)_3CH(OClO_3)CH_3 + CH_3(CH_2)_2CH(OClO_3)CH_2CH_3$$

Both alkyl perchlorates and alkyl triflates have been utilized as alkylating agents without separating them from the nonpolar solvents in which they were prepared.[2,7] Triflates are preferable for general synthetic use because of their somewhat greater reactivity and because they can be handled safely as neat materials. The reactions of commercially available silver perchlorate and silver triflate with alkyl iodides in appropriate solvents provide convenient and selective preparative routes to these potent alkylating agents. The methods would be expected to be applicable to other weakly nucleophilic anions. The silver salt reactions complement the reactions of alcohols with dichlorine heptoxide[2] and with triflic anhydride[7] as practical routes to perchlorates and triflates. Thus, the anhydride methods are superior for substrates with electron-withdrawing substituents since the halides are unreactive, whereas the silver reactions can be applied to reactive halogens where the corresponding alcohols are unstable.

Silver salt displacement reactions have been rationalized on the basis of ion-pair mechanisms with both silver ion and the displacing nucleophile participating in the transition state[8,9] or on the basis of a concerted push–pull mechanism.[10] The degree of participation by silver is envisioned as a function of the nucleophilic power of the anion, with poor nucleophiles requiring a greater degree of carbon–halogen bond breaking in the transition state. Perchlorate and triflate which are the least nucleophilic anions that have been used in silver salt displacements should require a relatively high degree of carbonium ion character in the transition state. These systems should therefore be more prone to isomerization than in the case of more nucleophilic anions.

The lack of isomerization in benzene can be rationalized on the basis of complexation of silver ions by the solvent. It is noteworthy that the reaction is significantly slower in benzene than in solvents such as carbon tetrachloride. It has been recognized that silver salt reaction rates are an inverse function of the complexing ability of the solvent.[9] The less active complexed silver ions would exert less "pull" on the leaving halogen, and the resulting transition state is more SN2 like. Since complexation is an equilibrium phenomenon, intermediate results in mixed solvents are to be expected. Where an excess of salt over the solubility is used, surface sites are subject to the same equilibrium deactivation. A factor contributing to the benzene effect may be increased reactivity of the anion in solution.

Kornblum and Hardies[10] observed retention of configuration in the reaction of silver nitrite or silver nitrate with α-phenethyl chloride in benzene but inversion in saturated hydrocarbons. The results were explained on the basis of a carbonium ion–benzene π complex which undergoes displacement by the anion. Inversion predominated for 2-octyl halides with these reactions as well as with the reaction of silver perchlorate in benzene.[9] The π complex mechanism thus appears applicable only to the more stable carbonium ions.

Experimental Section

Caution: Neat alkyl perchlorates are sensitive explosives and should be handled only with adequate protective devices. Dilute solutions are useable as reagents with previously noted precautions.[2]

General. Nmr spectra were recorded with a Varian T-60 spectrometer, and ir spectra were recorded with a Perkin-Elmer 700 spectrometer. Anhydrous grade silver perchlorate was dried azeotropically before use.[11] Silver triflate, prepared from triflic acid and silver oxide,[12] was dried by azeotroping with benzene until the salt was soluble; solvent was removed and the residue was dried for 5 hr at 80° (0.05 mm).

Reaction of Silver Perchlorate with Propyl Iodide. Propyl iodide (0.170 g, 1 mmol) was added with stirring to 0.207 g (1 mmol) of anhydrous silver perchlorate and 3 ml of carbon tetrachloride at 0°. After 1 hr, nmr analysis[2] of the solution, using chlorobenzene as a quantitative standard, showed a quantitative yield of a mixture of propyl perchlorate (40%) and isopropyl perchlorate (60%). Variations of up to 10% were observed in yields of the components but the total remained quantitative. Identical results were obtained using pentane or 1,1,2-trichlorotrifluoroethane as the solvent. Methylene chloride gave a 92% yield of a mixture of propyl perchlorate (62%) and isopropyl perchlorate (38%). In an experiment identical with that above using carbon tetrachloride, but with twice the theoretical amount of propyl iodide, the product consisted of 41% isopropyl perchlorate and 59% propyl perchlorate. Four times the theoretical amount of propyl iodide gave 23% isopropyl perchlorate and 77% propyl perchlorate.

The use of benzene as the reaction solvent required 18 hr of stirring at room temperature for completion. The benzene solution was filtered, washed with water, and dried over magnesium sulfate. Nmr analysis showed a 91% yield of propyl perchlorate and no trace of isopropyl perchlorate. The benzene solution was added to an equal volume of 10% lithium bromide in acetone and the mixture was washed with water and dried. Nmr and glpc showed propyl bromide but no isopropyl bromide. No rearrangement was observed when ten times the theoretical amount of silver perchlorate (2.07 g) was used, mainly out of solution.[13]

The reaction of equivalent amounts of propyl iodide and silver perchlorate for 18 hr, as above, in a solvent consisting of 33% benzene and 67% carbon tetrachloride gave a 90% yield of perchlorates consisting of 50% propyl perchlorate and 50% isopropyl perchlorate. A solvent consisting of 67% benzene and 33% carbon tetrachloride gave a 91% yield consisting of 15% isopropyl perchlorate and 85% propyl perchlorate.

Propyl perchlorate and isopropyl perchlorate were unchanged in control experiments in the presence of silver perchlorate and silver iodide.

Preparation of Alkyl Perchlorate Solutions. Equivalent amounts of silver perchlorate were reacted as above with methyl iodide, ethyl iodide, isopropyl iodide, allyl iodide, pentyl iodide, and hexyl iodide to give the corresponding perchlorates[2] with no detectable isomeric products. The respective solvents and yields are shown in Table I.

Reaction of Hexyl Iodide with Silver Perchlorate in Carbon Tetrachloride. The above procedure was used. Nmr analysis showed that the product consisted of 42% 1-hexyl perchlorate and 58% secondary perchlorates. In this mixture, 2-hexyl perchlorate and 3-hexyl perchlorate could not be resolved by nmr. The solution was added to an equal volume of 10% lithium bromide in acetone and the mixture was washed with water. A mixture of 2-bromohexane and 3-bromohexane was isolated by preparative glpc. Nmr analysis, by comparison with authentic samples, showed a 4:1 ratio of 2-bromohexane to 3-bromohexane. In control experiments, 1-hexyl perchlorate gave a quantitative yield of 1-bromohexane, and the secondary perchlorates each gave a 50% yield of the corresponding bromide.

Reaction of Silver Triflate with Propyl Iodide. Propyl iodide (0.170 g, 1 mmol) was added with stirring to 0.259 g (1 mmol) of

silver triflate in 3 ml of carbon tetrachloride at ambient temperature. Yields were determined after 2 hr by both proton and fluorine nmr using benzotrifluoride as a quantitative standard. A 97% yield of triflates was obtained consisting of 34% propyl triflate and 66% isopropyl triflate. The yields of the components varied ±10% but the total was always nearly quantitative. The same results were obtained using 1,1,2-trichlorotrifluoroethane or pentane as solvent. Methylene chloride gave a 95% yield consisting of 59% propyl triflate and 41% ispropyl triflate. Using benzene as solvent (18 hr) gave a 92% yield of propyl triflate with no isopropyl triflate. A solvent consisting of 33% benzene and 67% 1,1,2-trichlorotrifluoroethane gave a 98% yield containing 43% propyl triflate and 57% isopropyl triflate; 50% benzene and 50% 1,1,2-trichlorotrifluoroethane gave a 98% yield with 51% propyl triflate and 49% isopropyl triflate; 67% benzene and 33% 1,1,2-trichlorofluoroethane gave a 94% yield with 77% propyl triflate and 23% isopropyl triflate.

Propyl Triflate. A solution of 0.30 g (5 mmol) of propanol and 0.395 g (2 mmol) of pyridine in 5 ml of carbon tetrachloride was added dropwise with stirring to a solution of 1.41 g (5 mmol) of triflic anhydride in 10 ml of carbon tetrachloride at 0°. In 15 min the solution was filtered, washed with water, and dried over magnesium sulfate. Nmr analysis using chlorobenzene as a quantitative reference, showed an 86% yield of propyl triflate: proton nmr (CCl_4) δ 4.45 (t, 2 H, J = 6 Hz, CH_2O–), 1.83 (m, 2 H, CH_2CH_2O–), and 1.08 ppm (t, 3 H, J = 6 Hz, CH_3); fluorine nmr (CCl_4) ϕ 75.80 ppm (s); ir (CCl_4) 2990 (m), 1460 (w), 1420 (vs), 1250 (s), 1220 (vs), 1155 (vs), and 950 cm^{-1} (vs).

Preparation of Alkyl Triflate Solutions. By the procedure used above for propyl iodide, equivalent amounts of silver triflate were reacted with methyl iodide, ethyl iodide, isopropyl iodide, allyl iodide, pentyl iodide, hexyl iodide, and decyl iodide to give the corresponding triflates. The respective solvents and yields are shown in Table II.

Pentyl Triflate. Pentyl iodide (0.91 g, 4.6 mmol) was added dropwise with stirring to a partial suspension of 2.40 g (9.2 mmol) of silver triflate in 25 ml of benzene. The mixture was stirred 18 hr, filtered, washed with water, dried over magnesium sulfate, and distilled to give 0.785 g (82%) of pentyl triflate, bp 55–57 (1.5 mm), with spectra identical with those reported.[7]

Hexyl Triflate. Hexyl iodide (2.12 g, 10 mmol) was reacted with 2.57 g (10 mmol) of silver triflate in 50 ml of benzene as above to give 2.13 g (91%) of hexyl triflate, bp 26–28° (0.1 mm): proton nmr (CCl_4) δ 4.43 (t, 2 H, J = 6 Hz, CH_2O), 1.80 (m, 2 H, CH_2CH_2O), 1.26 (m, 6 H, CH_2), and 0.90 ppm (m, 3 H, CH_3); fluorine nmr (CCl_4) ϕ 75.8 ppm (s); ir (CCl_4) 1420, 1225, 1155, and 940 cm^{-1} (SO_3CF_3).

Anal. Calcd for $C_7H_{13}F_3SO_3$: C, 35.90; H, 5.59. Found: C, 35.81; H, 5.72.

Decyl Triflate. Decyl iodide (4.02 g, 15 mmol) was reacted by the above procedure with 5.14 g (20 mmol) of silver triflate in 100 ml of benzene. The washed and dried benzene solution was filtered through silicic acid and stripped of solvent to give 4.05 g (93%) of decyl triflate, a colorless oil: proton nmr ($CDCl_3$) δ 4.42 (t, 2 H, J = 6 Hz, CH_2O–), 1.82 (m, 2 H, CH_2CH_2O–), 1.27 (m, 14 H, CH_2), and 0.83 ppm (m, 3 H, CH_3); fluorine nmr ϕ 75.4 (s); ir (CCl_4) 1420, 1220, 1160, and 950 cm^{-1} (SO_3CF_3).

Anal. Calcd for $C_{11}H_{21}F_3SO_3$: C, 45.50; H, 7.29; S, 11.05. Found: C, 45.44; H, 7.09; S, 11.40.

Registry No.—Silver perchlorate, 7783-93-9; silver triflate, 2923-28-6; propyl triflate, 29702-90-7; propanol, 71-23-8; triflic anhydride, 358-23-6; pentyl triflate, 41029-43-0; hexyl triflate, 53059-88-4; decyl triflate, 53059-89-5; $CH_3(CH_2)_8CH_2I$, 2050-77-3.

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New Carbonyl Compounds from the Alkaline Ferricyanide Dehydrogenation of *p*-Cresol

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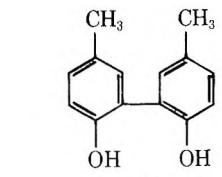
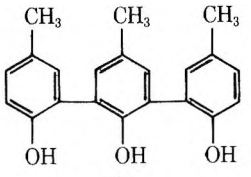
Pummerer's ketone type trimeric ketone **8** and tetrameric ketone **9** have been obtained from the dehydrogenation of *p*-cresol with alkaline ferricyanide in addition to **1**, **2**, **3**, and **4**. The tetrameric ketone **9** is apparently formed through dehydrogenation and subsequent intramolecular radical substitution of **10** which was produced by Pummerer's ketone type oxidative coupling of the diphenyl **1**. Trimeric hemiketals **6** and **7** obtained previously from the ferric chloride dehydrogenation of *p*-cresol and/or their derivatives were not found in the alkaline ferricyanide or peroxide–peroxidase dehydrogenation of *p*-cresol. It had been concluded that in the ferric chloride dehydrogenation hemiketals **6** and **7** were formed through acid-catalyzed hydration of **12**, which was produced by dehydrogenation and subsequent intramolecular radical substitution of **10**, rather than by subsequent acid-catalyzed reactions of **11**. Dehydration of **6** by general acid catalysis results in rearrangement of the molecule involving an intramolecular ether interchange by O-5 participation of the benzofuran oxygen, followed by dienol–benzene rearrangement to give **13**.

We previously reported that the dehydrogenation of *p*-cresol by the one electron transfer agent ferric chloride in acidic solution yielded three new ketonic products **5**–**7** and a dimeric ether **3** in addition to **1**, **2**, and Pummerer's ketone **4**.[2] In that communication we reported that **5** was isolated from the peroxide–peroxidase dehydrogenation of *p*-cresol but not hemiketals **6** and **7**. Compounds **1**, **2**, and **4** were isolated earlier from the ferric chloride,[3–5] alkaline ferricyanide[6] and peroxide–peroxidase[7] dehydrogenation of *p*-cresol.



1



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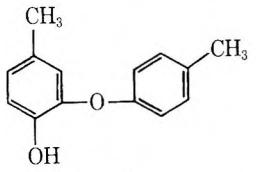

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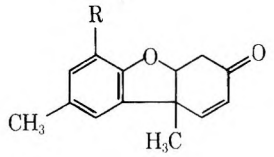
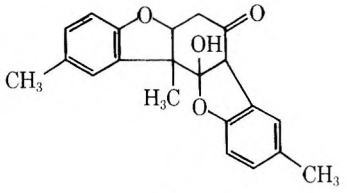


4, R = H
5, R = 2-hydroxy-5-methylphenyl



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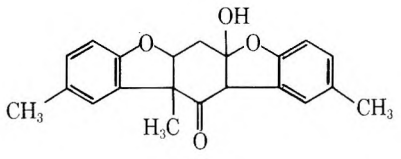

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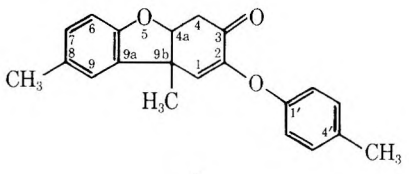

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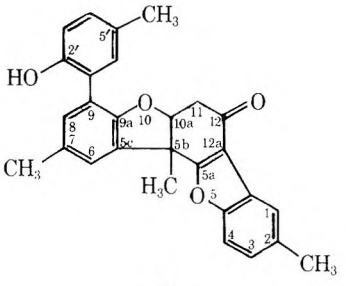
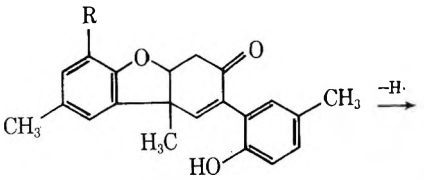


9

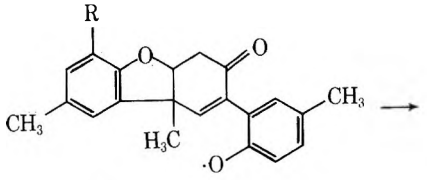
We have now reinvestigated the alkaline ferricyanide dehydrogenation of *p*-cresol which was previously reported by Haynes, *et al.*[6] In that communication it was reported that **1**, **2**, and **4** were isolated and that 32% nonketonic polymers of unknown structure were formed. In our present work, *p*-cresol in 0.4 *N* sodium carbonate solution was dehydrogenated with 1.5 equiv of potassium ferricyanide. During the reaction *ca.* 1.3 equiv of potassium ferricyanide was consumed. Two new ketonic products, 2-(4′-methylphenoxy)-4a,9b-dihydro-8,9b-dimethyl-3(4*H*)-dibenzofuranone (**8**) and 9-(2′-hydroxy-5′-methylphenyl)-5b,10a-dihydro-2,5b,7-trimethyl-12(11*H*)-benzo[1,2-*b*:3,4-*b*′]bisbenzofuranone (**9**) were isolated in addition to **1**, **2**, **3**, and **4**.

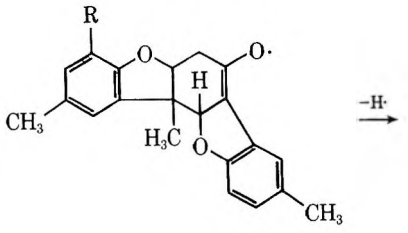
The ir spectrum of the trimeric ketone **8**, $C_{21}H_{20}O_3$ (M^+, *m/e* 320), indicated the presence of an α,β-enone (1690 and 1635 cm^{-1}), cyclic trisubstituted double bond (863 and 851 cm^{-1}), isolated and two adjacent aromatic hydrogens (880 and 805 cm^{-1}). The nmr spectrum showed that two geminal protons H-4, H-4a with H-1 constituted the characteristic ABMX system of Pummerer's ketone derivatives[2] with J_{AB} = 17.8, J_{AM} = 2.7, J_{BM} = 3.9, and J_{MX} = 1.8 Hz. The absence of H-2 signal indicated that **8** was a derivative of **4** with a substitutional group corresponding either to 4-methylphenoxyl or 2-hydroxy-5-methylphenyl group on C-2. The ir and uv spectra showed the absence of phenolic hydroxyl group in **8**. The mass spectrum exhibited ion peaks corresponding to M^+, M − 15, and M − 107 ions. Therefore, structure **8** for the trimeric ketone was apparent.

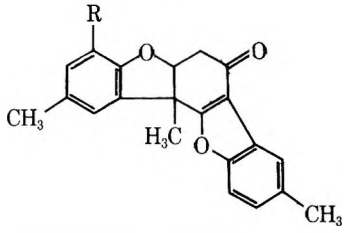
Chart I



10, R = 2-hydroxy-5-methylphenyl
11, R = H







9, R = 2-hydroxy-5-methylphenyl
12, R = H

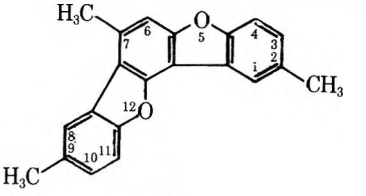
The tetrameric ketone **9**, $C_{28}H_{24}O_4$ (M^+, *m/e* 424), had two hydrogen atoms less than the expected tetrameric compound of *p*-cresol. The phenolic nature of the compound was indicated by the bathochromic shift observed in the uv spectrum when base was added. The ir spectrum showed the presence of a hydroxyl group (3320 cm^{-1}), a conjugated carbonyl (1652 cm^{-1}), isolated and two adjacent aromatic hydrogens (857 and 807 cm^{-1}). The nmr spectrum was consistent with the structure proposed for this compound. Two geminal protons H-11 and H-10a constituted an ABX system with J_{AB} = 17.8, J_{AX} = 2.9, and J_{BX} = 4.3 Hz. The absence of the α,β-enone olefinic H-5a and H-12a signals indicated that the benzofuran moiety was fused to **5** at C-5a and C-12a. The mass spectrum exhibited ion peaks corresponding to M^+ and M − 15 which is characteristic of Pummerer's ketone derivatives.[2]

The trimeric ketone **8** is formed through the Pummerer's ketone type ortho–para dehydrogenative coupling of *p*-cresol and **3**. Tetrameric ketone **9** is formed through intramolecular dehydrogenation–radical substitution–dehydrogen-

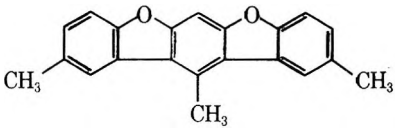
ation[8] of intermediate **10** which was formed through ortho–para dehydrogenative coupling of biphenyl **1**.

We previously postulated[2] that in the acidic ferric chloride dehydrogenation of *p*-cresol hemiketals **6** and **7** could be formed through addition of water to the α,β-enone portion of **11**, followed by oxidation of the resulting 1,3 ketol to the 1,3 dione and subsequent tautomerization and acid-catalyzed cyclization. However, this mechanism is not tenable in view of our present investigation. These hemiketals resulted from intermediate **12** which was formed by the intramolecular dehydrogenation–radical substitution–dehydrogenation of **11** in a manner analogous to the formation of **9** from **10**. Acid-catalyzed addition of water on the α,β-enone of **12** afforded the hemiketal **6** which underwent acid-catalyzed hydrolysis, tautomerization, and cyclization to give the isomeric hemiketal **7**.[9] This accounts for the absence of these hemiketals and/or their derivatives in the alkaline ferricyanide and peroxide–peroxidase dehydrogenation products of *p*-cresol (Chart I).

Dehydration of **6** with *p*-toluenesulfonic acid in toluene unexpectedly resulted in elimination of 2 mol of water to give the product **13**, $C_{21}H_{16}O_2$ (M^+, *m/e* 300). The ir spectrum of the product indicated the presence of 1,2,4-trisubstituted benzenes and an isolated aromatic hydrogen but the absence of hydroxyl and carbonyl groups. The uv spectrum showed very intense adsorption bands at λ_{max} 267 and 294 nm corresponding to the 250- and 280-nm bands of dibenzofuran.[10] The intensities of these bands are approximately twice those of the corresponding bands of dibenzofuran. The near constancy of $\epsilon/(n-1)$ for both bands observed in Table I is analogous to that of *m*-polyphenyls.[11] This indicates that the product has a *m*-terphenyl skeleton consisting of two dibenzofuran units with a common benzene ring. The nmr spectrum showed the presence of three aromatic methyl groups with one of them being deshielded, and seven aromatic hydrogens which constituted two separated ABX systems with J_{AB} = 8.0 and J_{BX} = 2.2 Hz and a singlet. The mass spectrum exhibited ion peaks corresponding to M^+ and M − 1 ions but not the characteristic M − 15 ion. There are two possible structures for the product. Structure **14** belongs to symmetry species point group C_{2v} with the C_2 axis bisecting the molecule into two equivalent parts and should give a nmr spectrum with a single ABX system in the aromatic region. This is not in agreement with the nmr spectrum obtained. The structure **13**,



13



14

2,7,9-trimethylbenzo[1,2-*b*:3,4-*b*′]bisbenzofuran is consistent with the spectral data discussed above (Chart II).

It is apparent that the dehydration of **6** by general acid catalysis results in rearrangement of the molecule involving an intramolecular ether interchange followed by dienol–benzene rearrangement to give **13**. Protonation and subsequent dehydration of **6** produces the carbonium ion **15** which would give **12** by deprotonation. However, the mesomeric effect of the benzofuran oxygen to the carbonium ion

Chart II

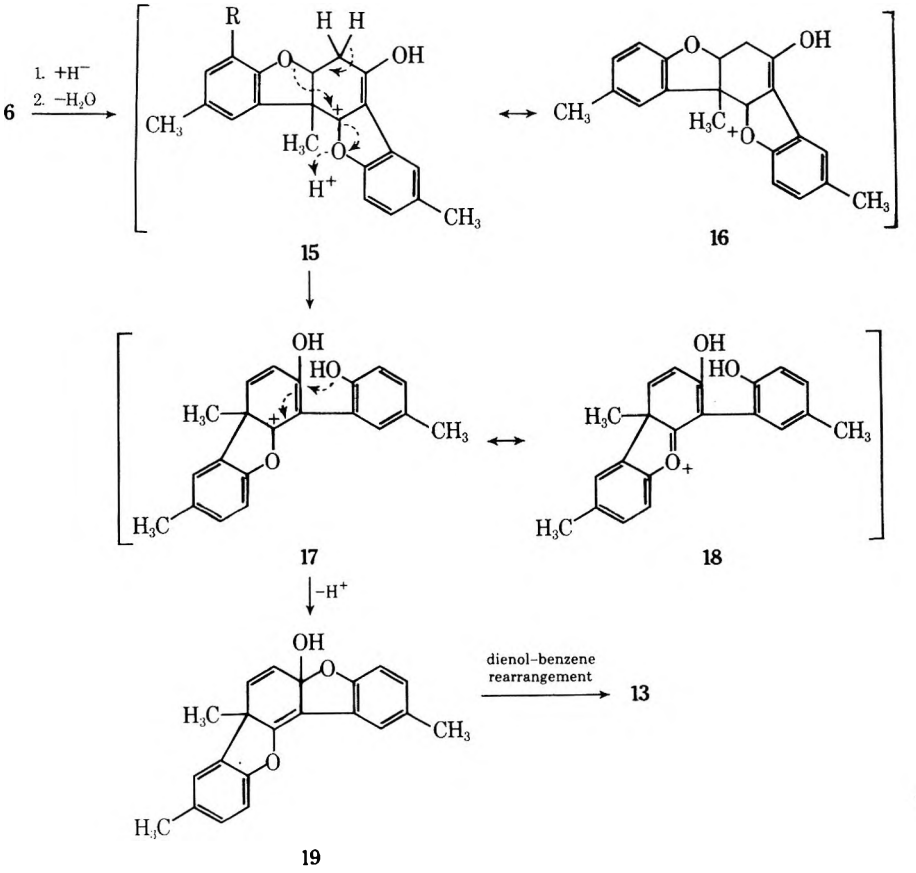


Table I

Compd	n^a	λ, nm	ε	ε/(n − 1)	λ, nm	ε	ε/(n − 1)
Dibenzofuran[b]	2	249	17,400	17,400	280	14,200	14,200
4-Methyldibenzofuran[b]	2	252	15,700	15,700	282	12,400	12,400
13	3	267	49,840	24,920	294	28,640	14,320

[a] *n* is the number of benzene rings. [b] Reference 10.

center in form **16** results in stabilization of the carbonium ion. Consequently, the equilibrium is in favor of the carbonium ion rather than the deprotonation under the reaction condition. This also prevents **15** from undergoing an alternative Wagner–Meerwein rearrangement which would lead to formation of **14** through subsequent acid-catalyzed retroaddition of α,β-enone, cyclization to hemiketal, and further dehydration. The carbonium ion **15** undergoes intramolecular ether interchange to give the carbonium ion **17** by O-5 participation of the second benzofuran oxygen.[12] Acid-catalyzed cyclization of **17** affords the hemiketal dienol **19** which undergoes dienol–benzene rearrangement to give **13**.

Experimental Section

Nmr spectra were obtained with a Varian HA 100 spectrometer, mass spectrum with an AEI MS-1201, ir with a Beckman 12 spectrophotometer, and uv with a Cary 15 uv spectrophotometer. Melting points were uncorrected.

Dehydrogenation of *p*-Cresol with Alkaline Ferricyanide. A solution of potassium ferricyanide (49.4 g) in 500 ml of water was added dropwise during an hour to a stirred solution of *p*-cresol (10.8 g) in 1 l. of 0.4 *N* sodium carbonate at room temperature. After 4 hr the reaction mixture was extracted with ether. Titration of the solution indicated that 1.32 equiv of ferricyanide had been consumed. The ether solutions was shaken with 1 *N* sodium hydroxide solution and was divided into alkali-soluble and -insoluble parts. A total of 6.2 g of alkaline-insoluble material was obtained.

The alkaline-insoluble material (5.8 g) was chromatographed on a silica gel column with chloroform–cyclohexane (4:1) as solvent to isolate **3**, **5**, **8**, and **9**.

2-Hydroxy-4',5-dimethyl Diphenyl Ether 3. This compound was isolated from the first fraction of the column chromatography and purified by preparative tlc on silica gel as an oil (56 mg). The identification of the compound was carried out by comparison of ir and nmr with authentic sample.[2]

Pummerer's Ketone 4. This compound was obtained from the second fraction and was recrystallized from methanol; colorless plates (2.1 g), mp 124–125° (lit.[2] 124–125°).

2-(4'-methylphenoxy)-4a,9b-dihydro-8,9b-dimethyl-3(4*H*)-dibenzofuranone (8). This compound was isolated and purified from the third fraction of the column chromatography in the same manner as **3**. The compound was recrystallized from methanol as colorless plates (36 mg): mp 102–103°; uv λ_{max} (methanol) 283 (sh), 296 nm; ir (KBr) 3020 (ArH), 2963, 2920, 2902, 2860 (CH_3 and CH_2), 1690, 1634 (α,β-enone), 1612, 1506, 1490 (phenyl), 1247, 1220 ($ArOCH_3$), 880, 863, 851, 824, 811, and 805 cm^{-1}; nmr ($CDCl_3$) τ 8.44 (s, 3, Anu–CH_3), 7.72 (s, 6, Ar–CH_3), 7.06 (m, 1, J = 17.8, 3.9 Hz, $OCH_MCH_AH_BCO$), 6.83 (m, 1, J = 17.8, 2.7 Hz, $OCH_MCH_AH_BCO$), 5.38 (m, 1, $ArOCH_MCH_AH_B$), 4.26 (d, 1, J = 1.8 Hz, $-CH_X{=}C-CO$), 3.40–2.90 (m, 7, ArH); ms *m/e* (rel int) 321 (26), 320 (M^+, 100), 306 (22), 305 (92), 290.7 (m*), 278 (5), 277 (17), 251.6 (m*), 213 (11), 198 (6), 186 (5), 185 (19), 160 (7), 159 (23), 146 (6), 145 (16), 129 (7), 128 (8), 115 (14), 91 (27), 77 (12), 65 (17).

9-(2'-Hydroxy-5'-methylphenyl)-5b,10a-dihydro-2,5b,7-trimethyl-12(11*H*)-benzo[1,2-*b*:3,4-*b'*]bisbenzofuranone (9). This compound was isolated and purified from the fourth fraction of the column chromatography in the same manner as **3**. The compound was recrystallized from methanol as colorless plate (18 mg): mp 219–220°; uv λ_{max} (methanol) 297 nm; λ_{max} (0.05 *N* CH_3ONa in methanol) 294 and 335 nm; ir (KBr) 3320 (OH), 3016 (ArH), 2974, 2958, 2910, 2893, 2860 (CH_3 and CH_2), 1652 (conjugated CO), 1614, 1583, 1510, 1488 (phenyl), 866 (sh), 857, 845, 821, 807 cm^{-1}; nmr ($CDCl_3$) τ 8.19 (s, 3, Anu–CH_3), 7.66 (s, 3, Ar–CH_3), 7.65 (s, 3, Ar–CH_3), 7.55 (s, 3, Ar–CH_3), 7.00 (m; 1, J = 17.8 and 4.3 Hz, $OCH_XCH_AH_BCO$), 6.81 (m, 1, J = 17.8 and 2.9 Hz, $OCH_XCH_AH_BCO$), 5.22 (m, 1, J = 2.9 and 4.3 Hz, $OCH_XCH_AH_BCO$), 4.94 (s, 1, eliminated by D_2O exchange, OH), 3.35 (d, 1, J = 8.0, Ar–H), 3.04 (m, 1, J = 8.0 and 2.2 Hz, Ar–H), 3.03 (d, 1, J = 8.0, Ar–H), 2.85 (m, 3, Ar–H), 2.73 (m, 1, J = 2.2 and 0.6 Hz, Ar–H), 2.13 (m, 1, J = 2.2 and 0.6 Hz, Ar–H); ms *m/e* (rel int) 425 (31), 424 (M^+, 100), 410 (20), 409 (56), 394.5 (m*), 382 (8), 381 (17).

2,7,9-Trimethylbenzo[1,2-*b*:3,4-*b'*]bisbenzofuran (13). A mixture of 5a-hydroxy-5a,5b,10a,12a-tetrahydro-2,5b,7-trimethyl-12(11*H*)-benzo[1,2-*b*:3,4-*b'*]bisbenzofuranone (**6**) (80 mg), *p*-toluenesulfonic acid (40 mg), and toluene (40 ml) was heated at reflux temperature with continuous slow removal of the solvent for 6 hr. After cooling, pyridine was added to the reaction mixture to neutralize the acid. The mixture in chloroform (100 ml) was washed with water, 0.5 *N* HCl, and again with water, dried, and evaporated *in vacuo*. The residue was recrystallized from chloroform–methanol to give colorless needles (36 mg), mp 164–166°; uv λ_{max} in chloroform 258, 267, 294, 309 (sh), and 323 nm (ε 32,000, 49840, 28640, 3910, and 7000); ir (KBr) 3052, 3020 (Ar–H), 2972, 2943, 2917, 2858 (CH_3), 1868, 1860, 1801, 1794, 1735, 1730 (sh), (1,2,4-trisubstituted benzene) 1653 (m, condensed aromatic ring), 1612, 1589, 1480, 1469, 1458, 1440 (phenyl and benzofuran), 869, 858 (isolated Ar–H), 820, 795 (two adjacent Ar–H) cm^{-1}; nmr ($CDCl_3$) τ 7.64 (s, 6, Ar–CH_3), 7.13 (s, 3, Ar–CH_3), 2.76 (m, 2, J = 8.0 and 2.2 Hz, Ar–H), 2.68 (s, 1, Ar–H), 2.54 (d, 1, J = 8.0 Hz, Ar–H), 2.43 (d, 1, J = 8.0 Hz, Ar–H), 2.21 (d, 1, J = 2.2 Hz, Ar–H), 1.97 (d, 1, J = 2.2 Hz, Ar–H); ms *m/e* (rel int) 301 (23), 300 (M^+, 100), 299 (31), 288 (m*).

Acknowledgments. The authors are indebted to Messrs. M. W. Wesolowski and L. C. Zank of the Forest Products Laboratory for recording nmr and ir spectra.

Registry No.—**1**, 15519-73-0; **3**, 10568-14-6; **6**, 53042-29-8; **8**, 53042-30-1; **9**, 53042-31-2; **13**, 53042-32-3; *p*-cresol, 106-44-5; potassium ferricyanide, 13746-66-2; dibenzofuran, 132-64-9; 4-methyldibenzofuran, 7320-53-8.

References and Notes

(1) (a) Part of this work was carried out at Ruhr-University Bochum, 463 Bochum-Querenburg, West Germany, (b) North Carolina State University, (c) Forest Service, U.S. Department of Agriculture. (d) Maintained at Madison, Wis., in cooperation with the University of Wisconsin.
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Dianilino Derivatives of Squaric Acid

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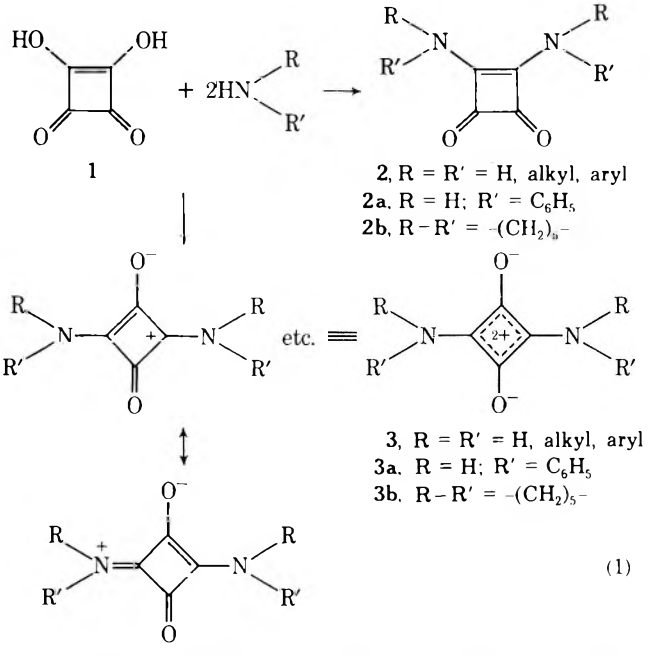
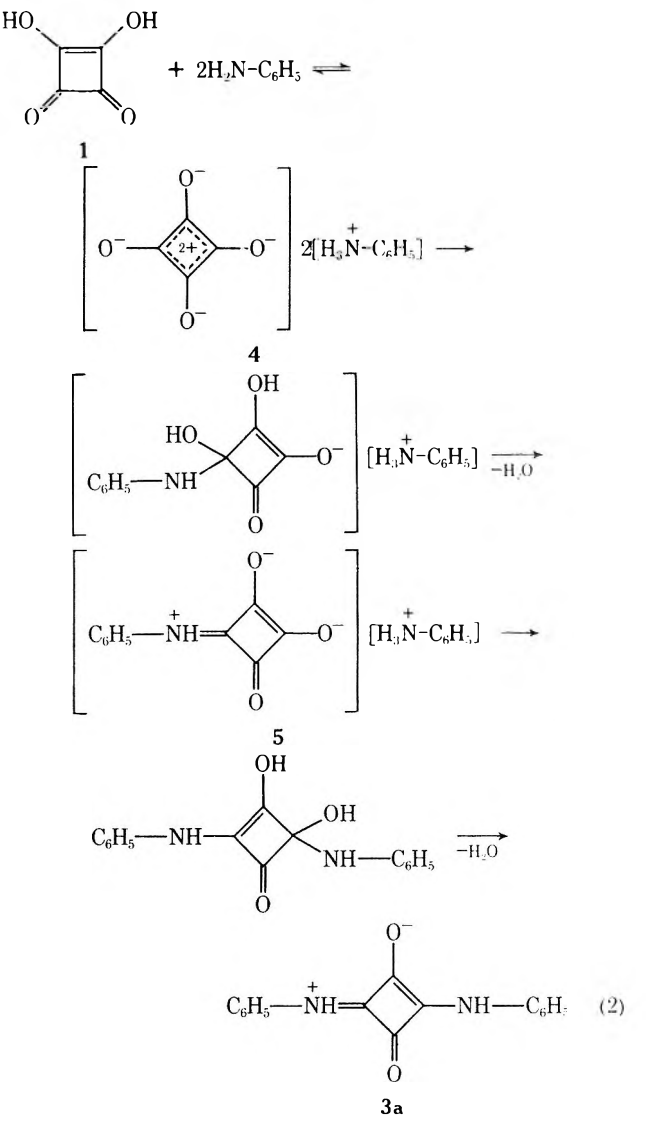
The reaction of squaric acid (1,2-dihydroxycyclobutene-3,4-dione) with aniline in *N,N*-dimethylformamide and other solvents produces not exclusively the 1,3-dianilino derivative (1,3-dianilinocyclobutenediylium 2,4-diolate, **3a**), as was maintained in the earlier literature, but additionally furnishes the 1,2-dianilino isomer (1,2-dianilinocyclobutene-3,4-dione, **2a**). The **3a**:**2a** isomer ratio is found to depend on the acidity of the medium; the ratio decreases as the solvent acidity is enhanced. The proposed mechanism accounting for the concurrent formation of both isomers involves the intermediacy of anilinium anilinosquarate (**5**) in dissociation equilibrium with anilinosquaric acid (**7**) and its conjugate base, anilinosquarate anion, with both acid and anion implicated as substrates in the further nucleophilic attack steps leading to the two dianilino isomers. The reaction of squaric acid with piperidine is also briefly investigated.

Considerable attention has been focussed for some time on the substitution behavior of squaric acid **1** (1,2-dihydroxycyclobutene-3,4-dione) and some of its derivatives.[1] Reactions involving "amidation" through substitution of one or both hydroxy groups of **1** with primary and secondary amines have occupied special interest. There is consensus in the earlier literature[1b,2,3] that diamidation reactions, far from producing the "regular" 1,2-diamino derivatives **2**, proceed exclusively with formation of the 1,3-diamino compounds **3** frequently depicted by cyclobutenediylium 2,4-diolate structures[1b,2b-d,3] as shown[4] (eq 1).



(1)

The most comprehensive study of this topic, employing the reactant pair squaric acid/aniline, was conducted by Gauger and Manecke.[3] These authors, condensing the two compounds in a molar ratio of 1:2 in boiling *N,N*-dimethylformamide (DMF) over a 1.5-hr period (substrate concentration 1 mol l^{-1}), obtained **3a** (74%) as the sole product. This formation of **3a** (and other 1,3-diamino compounds derived from different amines) was reported to be catalyzed by protonic acids.[2a,3] The reaction, as formulated in eq 2, was postulated[3] to involve the intermediacy of dianilinium squarate (**4**) and the anilinium salt **5** of anilinosquaric acid (1-anilino-2-hydroxycyclobutene-3,4-dione, **7**). The two workers prepared the salt **4** independently from **1** and aniline (1:2 molar ratio; first step in eq 2) and demonstrated the conversion of **4** to **5** under mild conditions; they further reported the transformation of **5** to **3a** in boiling



(2)

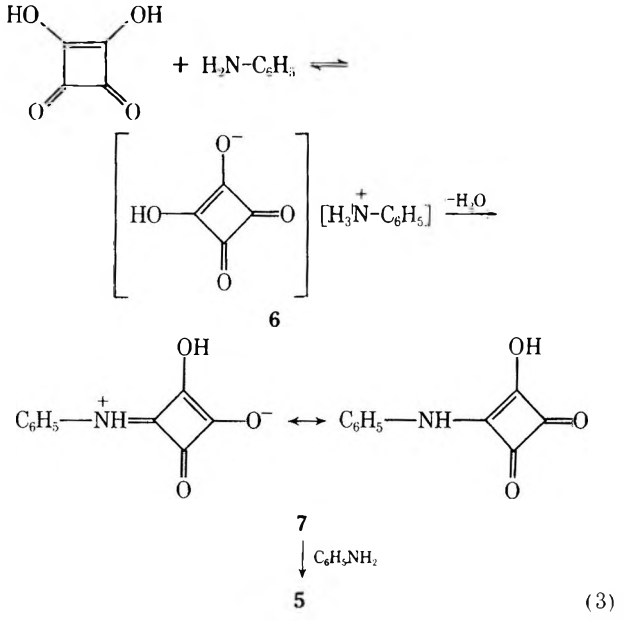
DMF in support of the scheme (eq 2) proposed. In the same work,[3] the structure of **5** was ascertained by the independent preparation of this salt from anilinosquaric acid (**7**) and aniline; **7** in turn was synthesized from equimolar quantities of **1** and aniline *via* the acidic salt **6** (eq 3).

Preliminary work in our laboratory showed more recently[6b] that the reaction of **1** and aniline is less straightforward than indicated by the proposed path of eq 2. It was found[6b] that under various experimental conditions, including those selected by Gauger and Manecke[3] and by Sprenger,[2e] the formation of **3a**, while predominant, is ac-

Table I
Anilino and Piperidino Derivatives of Squaric Acid[a]

Expt no.	Substrate	Nucleophile	Molar ratio substr/nucl	Substrate concn, mol l.$^{-1}$	Time, min.	Temp, °C	Product yields, %[b] 2a	3a	5	Isomer ratio[b] 3a:2a
1	Squaric acid (**1**)	Aniline	1:2	1.0	90	145 ± 1	17[c]	56[c]	17[d]	3
2	Squaric acid (**1**)	Aniline	1:2	1.0	5	145 ± 1	12[e]	40[e]	42	3
3	Squaric acid (**1**)	Aniline	1:2	1.0	10	145 ± 1	16	49	*f*	3
4	Squaric acid (**1**)	Aniline	1:2	1.0	90	100 ± 3	13	54	*f*	4
5	Squaric acid (**1**)	Aniline	1:2	1.0	90	70 ± 3	5	35	45	7
6	Squaric acid (**1**)[g]	Aniline[g]	1:2	0.8	60	60 ± 2		15	83	*f*
7	Squaric acid (**1**)	Aniline	1:2	0.2	240	62 ± 1		19	67[h]	*f*
8	Anilinosquaric acid (**7**)	Aniline	1:1	1.0	90	145 ± 1	17[i]	53[i]	*f*	3
9	Anilinosquaric acid (**7**)	Aniline	1:1	0.5	5	145 ± 1	13[i]	39[i]	*f*	3
10	Anilinosqauric acid (**7**)	*p*-Nitroaniline	1:1	0.5	5	145 ± 1	2[j]	9[k]	70[l]	4.5[o]
11	Squaric acid (**1**)	Piperidine	1:2	1.0	90	144 ± 1	0.1[m]	3.2[n]		32[o]
12	Squaric acid (**1**)	Piperidine[p]	1:32[p]	0.34	600	99 ± 1	0.0[m]	94[n,q]		∞[o]

[a] Reactions conducted in DMF (methanol in experiment 7; piperidine in experiment 12. [b] Rounded off to integral values except in experiments 11 and 12. Estimated maximum absolute error in yield determination: ±2% in 35–90% range; ±1.5% in 10–20% range; ±0.5% in 2–5% range; ±0.1% for **2b** in experiment 11. [c] Yields obtained under identical experimental conditions in ref 6b were 18 and 55%, respectively (74% **3a** only in ref 3). [d] In addition, 7% **12b**. Unchanged product yields at substrate concentration of 0.5 mol l.$^{-1}$. [e] Similar product yields at substrate concentration of 0.5 mol l.$^{-1}$. [f] Not determined. [g] Similar product yields with **4** in place of **1** and aniline. [h] In addition, 3% **4**. [i] Unchanged product yields with 1 mol of H_2O added to reconstitute conditions of experiment 1. Same results with **5** in place of **7** and aniline. [j] 1-Anilino-2-*p*-nitroanilinocyclobutene-3,4-dione (**13a**). [k] 1-Anilino-3-*p*-nitroanilinocyclobutenediylium 2,4-diolate(**13b**). [l] Recovered **7**. In addition, 73% *p*-nitroaniline recovered. [m] 1,2-Dipiperidinocyclobutene-3,4-dione (**2b**). [n] 1,3-Dipiperidinocyclobutenediylium 2,4-diolate (**3b**). [o] Isomer ratio **13b**:**13a** in experiment 10; **3b**:**2b** in experiments 11 and 12. [p] Two moles of nucleophile added as piperidinium chloride (remainder as free base) to conform to literature prescription (ref 2e). [q] Yield obtained under identical experimental conditions in ref 2e was 61%.

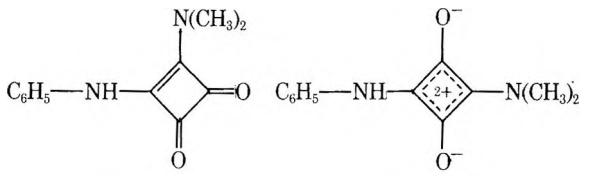


(3)

companied invariably by that of **2a** (eq 1), yields of the latter ranging from about 3 to 18%. As the substituent orientation in squaric acid diamidation proved of considerable interest to us in connection with polymerization studies,[7] we have continued and extended our earlier investigation of this problem, again using the reactant pair squaric acid/aniline, in an effort to cast some light on the mechanism underlying the two competing substitution reactions.

Results and Discussion

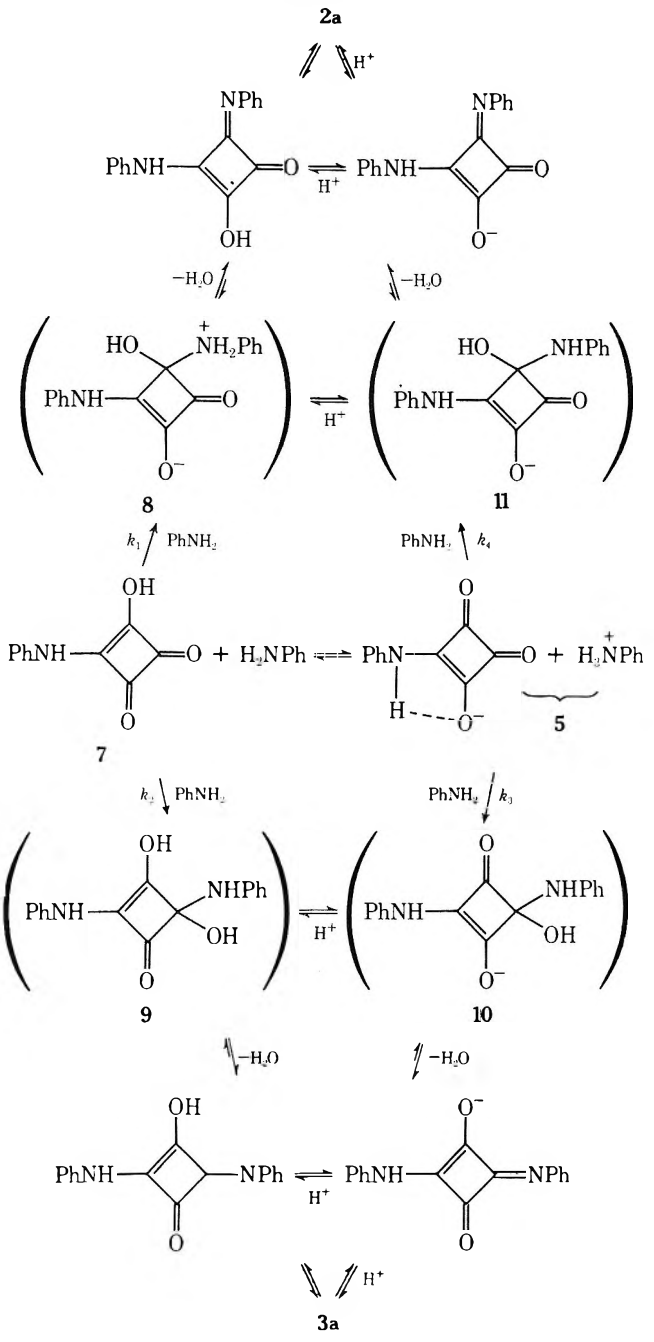
In a series of experiments, squaric acid and aniline (molar ratio 1:2) were allowed to react in solution at temperatures ranging from 60 to 146°. DMF was chosen as the solvent throughout to permit direct comparison with the pertinent earlier work[2a,c,d,3] conducted in this medium. In the first experiment, performed over a 1.5-hr period at the reflux temperature of the solvent (146°), we duplicated the conditions selected by Gauger and Manecke[3] and employed them later in our own work.[6b] The results, summarized in Table I (experiment 1), confirm our previous findings, yields of **2a** and **3a** being about 17 and 56%. In addition, we isolated the intermediary salt **5** (17%) and the by-product **12b** (7%), the latter resulting from solvent acylation at the



boiling temperature as in previous investigations.[6,8] With reflux time restricted to 5 min, other factors being equal (experiment 2), yields of the two dianilino compounds were 12 and 40% respectively; within the rather large experimental error limits (Table 1) inherent in the method of separation, this indicates a **3a:2a** isomer ratio identical with that in experiment 1. The same isomer ratio resulted from experiment 3, in which a 10-min reflux period was employed. The major product in experiment 2 was salt **5** (42%), which also represented the main product in some reactions conducted at lower temperatures, *e.g.*, experiments 6 (83%) and 7 (67%; in methanol). No significant changes in yield and product distribution resulted in these two experiments from the use of **4** in place of **1** and aniline in the proper stoichiometry.

The smooth early stage formation of the monocondensation product **5** from **4**, as well as directly from **1** and aniline, and its consumption in advanced stages of the condensation support the reaction scheme proposed by Gauger and Manecke[3] (eq 2) with respect to the formation of **3a**. Yet the results suggest the intermediacy of **5** not only in the sequence leading to **3a** but in the path leading to **2a** as well. Indeed, reactions performed with **5** or an equimolar mixture of **7** and aniline gave yield data for both **2a** and **3a** well coincident, within experimental error limits, with those in the corresponding runs starting with the 1:2 squaric acid/aniline reactant pair (compare experiments 8 and 9 with 1 and 2). On these grounds we accept the function of **5** (equil-

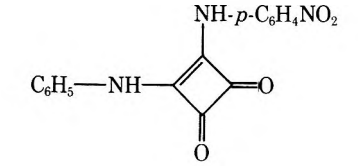
Scheme I



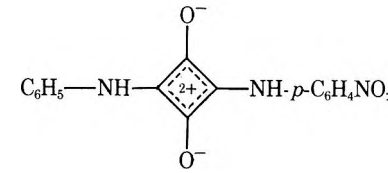
ibrating with **7** and aniline) as a common precursor of both **2a** and **3a.**

Accounting for the generation (from **5** or **7**) of the two dianilino compounds in the isomer ratios determined would be a straightforward matter if the reactions were thermodynamically controlled, as the product yield ratios should then simply correspond to the equilibrium isomer mixtures under the particular conditions of temperature and concentration. Yet the identical isomer ratio in experiments 1, 2, and 3 despite the wide range of heating periods suggests thermodynamic control to be highly unlikely. Equilibration experiments (see Experimental Section) in fact clearly show that, under the conditions of our condensation reactions in DMF medium, equilibrium control did not obtain, as no isomer interconversion was observed.[10]

Accepting kinetically controlled formation of the two isomers, we propose the following reaction scheme (Scheme I). The acid **7**, in the presence of aniline, exists in a rapidly establishing ionization equilibrium with **5**.[11] Attack by the aniline nucleophile (equilibrating with its conjugate acid) can now occur at C-2 and C-3 of both **7** and its anion in the product-determining step.[12] Each substrate species may, hence, produce both **2a** and **3a** along competitive reaction pathways. Considering first the acid **7**, which retains the vinylogous system of squaric acid and so allows for appreciable accumulation of positive charge on C-2, we predict fast attack at position 2 of the ring, giving rise to the formation of **2a** *via* the hypothetical adduct **8**. A second route, in which **9** is implicated as an intermediate, will produce **3a** through attack at C-3 of the polarized carbonyl group. Since any positive charge developing on C-3 is largely delocalized onto C-1 in this enone system, we expect step **7** → **9** to be slower than **7** → **8** despite steric preference of the former step for adduct formation; hence $k_1 > k_2$. The net result of the two concurrent reaction sequences then will be the predominant formation of the 1,2-dianilino compound and a minor yield of the 1,3-isomer. This inference presupposes the first, adduct-forming steps (approach of the nucleophile) to be rate determining, as can reasonably be expected for a vinylogous substitution reaction[14] and becomes in fact apparent from the appreciable retardation observed when a weak nucleophile, such as *p*-nitroaniline, is used in place of aniline in this step. Experiment 10, for example, in which **7** was treated with an equimolar quantity of the *p*-nitro compound for 5 min in boiling DMF, afforded only 11% combined yield of the two diamide isomers, **13a** and **13b,** whereas the corresponding run employing aniline (experiment 9) gave rise to 54% of combined **2a** and **3a.** The two reaction paths originating from **7** in fact are quite analogous to those leading to **2a** and **3a** in the recently described amidation of squaric esters,[6a] in which rate-controlling adduct formation by attack of aniline nucleophile on 1-anilino-2-alkoxycyclobutene-3,4-dione (counterpart of **7** in this scheme) was similarly established.



13a



13b

Superimposed on this pattern of pathways **7** → **2a** and **7** → **3a** now are the two reaction sequences arising from the anilinosquarate anion. While attack at C-2 (more retarded here because of reduced net positive charge on both C-2 and the equivalent C-4) will furnish **2a** as before, the faster reaction (rate-controlling adduct formation again being assumed) will involve attack at the more positive[15] (and sterically favored) C-3, giving rise to **3a** *via* **10**; *i.e.*, $k_3 > k_4$. Hence, the net result of the two reactions originating from anilinosquarate anion will be a predominant yield of the 1,3-isomer and a minor one of the 1,2-disubstituted compound.

Which one of the isomers now, with all four concurrent routes taken into consideration, exhibits net preponderance over the other, and to what extent, should largely depend on the relative equilibrium populations of **7** and its conjugate base and, hence, should be a function of the acidity of the medium. The outstandingly high acid strength

Table II
Anilino Derivatives of Squaric Acid in Media of Different Acidity

Expt no.	Molar ratio squaric acid/aniline	Solvent[a]	Squaric acid concn, mol l.$^{-1}$	Time, min.	Temp, °C	Product yields, %[b] 2a	3a	Isomer ratio[c] 3a:2a
13	1:2	DMF/pyridine (5:2)	0.7	90	126 ± 1	6	70	12
1[d]	1:2	DMF	1.0	90	145 ± 1	17	56	3
14	1.1:2	DMF	1.0	90	145 ± 1	21	52	2
15	1:2	DMF/10 *M* HCl (31:1)	1.0	90	140 ± 1	27	48	1.8
16	1:2	DMF/10 *M* HCl (19:1)	0.7	90	134 ± 1	40	25	0.6
17	1:2	AcOH/TFA[e] (9:1)	1.0/0.5[f]	120	113 ± 1	29	6	0.2

[a] All ratios by volume. [b] Rounded off to integral values. [c] Rounded off to integral values except in experiments 15–17. [d] Reentered from Table I. [e] Glacial acetic acid/trifluoroacetic acid. [f] Initial concentration 1.0 mol l.$^{-1}$, reduced to 0.5 mol l.$^{-1}$ after 30 min for improved stirrability.

(pK_a = 0.37) of 1-phenylsquaric acid (1-phenyl-2-hydroxycyclobutene-3,4-dione) is on record,[16] as is[3] the high acidity of the 1-anilino analog **7**. At the squaric acid/aniline molar ratio of 1:2 employed in the experiments presented (numbers 1–7), it is, therefore, safe to expect the dissociation equilibrium to be appreciably on the side of the anilinosquarate anion in the highly polar (ϵ = 38) and strongly cation-solvating medium.[17] As a result, **3a** should be the principal product of amidation in these experiments, as was, in fact, observed. One should, furthermore, expect k_4 to decrease comparatively faster than k_3 as the reaction temperature is lowered, a higher activation energy being associated with the step leading to **11** than with the one affording **10**. Again, this is borne out by the experimental results, an increase in the **3a:2a** isomer ratio being apparent as one goes from experiments 1 to 4 to 5 conducted at 146, 100, and 70°, respectively. Another trend corroborating the reaction pattern of Scheme I can be found in the variation of the isomer ratio with the acidity of the medium. In a series of experiments (Table II) conducted in DMF, the acidity was varied relative to experiment 1, taken as the standard here, through the addition of pyridine (experiment 13), on the one hand, and of increasing quantities of acidic compounds (**1** in experiment 14; hydrochloric acid in experiments 15 and 16), on the other. A drastic decrease of the **3a:2a** isomer ratio with increasing solvent acidity is qualitatively apparent from the tabulated data and is further reflected in the yield data of experiment 17 performed in the altogether different and even more acidic solvent, acetic/trifluoroacetic acid. In acidic media, clearly, the ionization of **7** is suppressed powerfully enough to render the two reaction sequences originating from **7** more important or even predominant. As a result, the reaction described by the sequence anilinosquaric acid → **8** → **2a** now progressively overrides the one of sequence anilinosquarate anion → **10** → **3a** with increasing acidity, and **2a** ultimately arises as the major product of condensation.

It is of interest to compare the reactivity of aniline with that of the more basic (but less nucleophilic) piperidine in condensation reactions with **1**. The squaric acid/piperidine reactant pair (1:2; conditions of experiment 1) gave little more than 3% of dipiperidino products **2b** and **3b** (experiment 11). These results confirm previous reports by Gauger and Manecke,[2a,d] who found piperidine similarly unreactive, the high basicity of this aliphatic amine rendering the intermediary dipiperidinium squarate too stable for smooth further condensation. The high **3b:2b** product ratio in this experiment is, of course, what one expects for a mechanism in which the primary adduct-forming steps are rate controlling as assumed for the aniline case in Scheme I, because only then can the amine's low nucleophilicity and concomitantly enhanced selectivity bear effectively on the utilization of the path of lowest activation energy (1,3-disubstitution) in the medium employed. Another reaction, duplicating Sprenger's work,[2e] was conducted in excess piperidine as the solvent (experiment 12). In agreement with Sprenger's results, we found the 1,3-disubstituted compound (**3b**) to be the sole product (94%) under these conditions. This finding, again, supports the proposed reaction pattern of Scheme I, the ionization equilibrium of the intermediary piperidinosquaric acid (counterpart of **7**) being so far to the right in the strongly basic environment as to prevent observable participation of the free acid as a substrate. At the same time, the high product yield in this experiment reflects the availability of unprotonated nucleophile, contrasting these conditions favorably with those in experiment 11.

The results here presented with aniline and piperidine as nucleophiles can be summarized as follows: (i) there is no evidence of proton assistance in the 1,3-diamidation of squaric acid; (ii) the 1,3-diamino compounds are not by necessity the exclusive products of amidation, the corresponding 1,2-diamino isomers generally being formed as well; (iii) the substitution orientation in squaric acid amidation depends decisively on both the amine's nucleophilicity and the acidity of the medium, although the effect of the latter is doubtlessly more complex than indicated in the simplified scheme proposed.

Experimental Section[18]

Squaric acid (**1**) was used as received (Chem. Werke Hüls AG). Aniline, *p*-nitroaniline, and piperidine were dried with Linde Molecular Sieves Type 4A and distilled under reduced pressure prior to use. *N,N*-Dimethylformamide (DMF), predried with Molecular Sieves, was distilled from CaH_2 under reduced pressure. Methanol was dried with Na and distilled. All glassware was dried, and reactions were conducted with moisture protection. Unless stated otherwise, solvent evaporation was conducted in a rotating evaporator at 20 ± 3° (0.05 Torr), and products were dried for 10–16 hr at 20 ± 3° (0.1 Torr) over P_2O_5. Thin-layer chromatography (tlc) was performed on precoated plates, Merck Silica Gel F-254, in ethyl acetate (4:1 ethyl acetate/ethanol for **2a**).

Monoanilinium Squarate (6). The literature procedure[3] (evaporation of an equimolar solution of **1** and aniline in ethanol/water) proved unsatisfactory in our hands, as salt formation (65.7%) was accompanied by amidation (14%). Although higher yields of the salt resulted from use of DMF solvent under otherwise similar conditions, the most satisfactory results were obtained by the following modification. The solution of 0.57 g (5 mmol) of **1** in 3 ml of DMF was cooled in a Dry Ice–acetone bath. A solution of 0.93 g (10 mmol) of aniline in 2 ml of DMF, precooled in the same fashion, was added, followed by the addition of cold ether (20 ml). The mixture was allowed to stand for 10 min in the cold bath. The crystallized solids were then removed by rapid filtration, washed with cold ether (5 ml), and dried under the conventional conditions. The crude salt, 1.0 g (96.6%), showing the correct ir spectrum for **6**, was recrystallized by dissolving it in DMF at room temperature,

adding ether to beginning turbidity, and allowing the salt to crystallize at −8°. The crystals were filtered off, washed with ether, and dried as before.

Anal. Calcd for $C_{16}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.93; H, 4.45; N, 6.00. 7.44.

Ir (KBr): 3020 m (ν_{OH}, bonded); 2850, 2600 s (ν_{N^+H}); 1800 m, 1650 s (ν_{CO}[19]); 1440–1600 s (δ_{N^+H}; $\nu_{C=C}$; "anilino" bands); 745 s (ν_{11}, phenyl; at 747 cm^{-1} in anilinium chloride); 715 m (δ_{CO}, hydroxycyclobutene-3,4-dione system[20]); 690 cm^{-1} m (ν_4, phenyl; at 685 cm^{-1} in anilinium chloride).

Pure **6**, when allowed to stand for 10 days in the open at room temperature, underwent partial condensation to **7**, which could be extracted with ether.

Dianilinium Squarate (4). Attempts to prepare this salt from **1** and aniline in methanolic solution by a literature procedure[3] failed, since the reaction invariably proceeded to the stage of **5**. At −70°, **4** was formed under more favorable conditions; yields were low (10–15%), however, as crystallization from the methanolic solution, induced by the addition of excess ether, remained incomplete. In the following procedure, which proved satisfactory, 0.93 g (10 mmol) of aniline was added to the solution of 0.57 g (5 mmol) of **1** in 100 ml of water, and the solution was immediately evaporated to dryness at 20° (0.1 Torr). The crystalline residue of crude monohydrate of **4** (no **5** or **3a** were present as shown by absence of ir absorption near 1800 cm^{-1}) was dried as before; yield 1.56 g (98%). For purification, 0.20 g of the monohydrate was dissolved in 10 ml of water, and the filtered solution was concentrated to 1 ml by isothermal distillation into P_2O_5 at 22° (0.1 Torr). The crystallized salt was washed with water (0°) and dried; yield 0.15 g.

Anal. Calcd for $C_{16}H_{16}N_2O_4 \cdot H_2O$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.43; H, 5.69; N, 8.42.

Ir (KBr): 3360 m (H_2O); 2910, 2600 s (ν_{N^+H}); 1440–1600 s (δ_{N^+H}; ν_{CO} and $\nu_{C=C}$; "anilino" bands), 745 s (ν_{11}, phenyl), 687 cm^{-1} m (ν_4, phenyl).

The monohydrate was also obtained by use of an equimolar mixture of **6** and aniline as reactants under otherwise identical conditions; crude yield, 98.5%.

For dehydration to **4**, the monohydrate was dried for 1.5 hr at 60° (0.05 Torr) over P_2O_5.

Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.64; H, 5.41; N, 8.90.

Ir (KBr): 2920, 2850 (d) m, 2600, 2510 (d) m (ν_{N^+H}); 1420–1600 s (δ_{N^+H}, ν_{CO} and $\nu_{C=C}$; "anilino" bands); 739 s (ν_{11}, phenyl); 689 cm^{-1} m (ν_4, phenyl).

Anilinium Anilinosquarate (5). Preparation of **5** by the described procedure[3] (heating the methanolic solution of **4** for 2 hr at reflux) proved impracticable, large quantities of **2a** and **3a** being formed under these conditions. Acceptable yields were obtained at room temperature as follows. To the solution of 1.14 g (10 mmol) of **1** in 50 ml of methanol was added 1.86 g (20 mmol) of aniline, and the solvent was removed over a 10-min period at 20° (0.5 Torr). The crystalline residue was taken up in warm (50°) water (500 ml). The solution was allowed to stand briefly at room temperature and was then filtered for removal of some diamidation products. Stepwise solvent evaporation at 25° to a final volume of 15 ml, each step followed by cooling to 5°, produced several ir-identical fractions of **5** in a combined yield of 2.51 g (89%) of dried product.

Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.87; H, 4.90; N, 9.59.

Ir (KBr): 3180 m (ν_{NH}); 2880, 2580 m (ν_{N^+H}); 1780 m, 1645 m–s (ν_{CO}); 1410–1600 s (δ_{NH}; δ_{N^+H}; $\nu_{C=C}$; "anilino" bands); 758, 743 m (ν_{11}, phenyl of anilino and anilinium, respectively); 690 cm^{-1} m (ν_4; both phenyl groups).

The final mother liquor furnished 0.012 g (0.4%) of **4**.

Anilinosquaric Acid (7). The compound was prepared by heating salt **6** for 20 min at 200 ± 5° as described.[3] The crude product was taken up in water (40 ml for 0.1 g of solid), and the filtered solution was concentrated to one-third its volume at 80° under reduced pressure. A major portion of the acid crystallized at 20°. Additional fractions crystallized upon further concentration and cooling of the mother liquor. The combined and dried, ir-identical fractions were obtained in 65% yield (lit.[3] 96.5%); dec range 265–275°.

Anal. Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.76; H, 3.50; N, 7.59.

Ir (KBr): 3210 m (ν_{NH}); 2680 m (ν_{OH}, bonded); 1820 m, 1685 s (ν_{CO}); 1400–1625 s (δ_{NH}; $\nu_{C=C}$; "anilino" bands); 760 s (ν_{11}, phenyl); 707 m (δ_{CO}[20]); 690 cm^{-1} m (ν_4, phenyl).

Condensation to **7** was similarly accomplished by heating **6** in DMF solution (1 *M*) for 2 hr at 60 ± 2°. The product crystallizing after the addition of excess ether at −70° was recrystallized from water as before; yield 52.4%. From the water-insoluble portions, a mixture of **2a** and **3a** was obtained in 12.4% yield.

1,2-Dianilinocyclobutene-3,4-dione (2a), and 1,3-Dianilinocyclobutenediylium 2,4-Diolate (3a). (a) From Squaric Acid (1) and Aniline, in DMF (Experiments 1–6). The following procedure, describing experiment 1, Table I, is representative of the amidation reactions of **1** with aniline conducted in DMF.

To the solution of 0.57 g (5 mmol) of **1** in 5 ml of DMF was added 0.93 g (10 mmol) of aniline, and the mixture was heated for 90 min under reflux. During this period, the dianilino compounds partially crystallized from solution. Separation of the products was completed by the addition of 20 ml of water to the hot reaction mixture. The yellowish solid, removed by filtration from the cooled mixture, was thoroughly washed with warm (50°) water to remove admixed **5** (washings combined with main filtrate) and was then extracted with four 15-ml portions of hot (60°) methanol. The combined methanol extracts, on gradual concentration, furnished 0.020 g of **2a** (included in total yield of **2a**, below), followed by 0.066 g (6.1%) of the more soluble **12b**, mp 273.5–274° (from methanol; mp undepressed on admixture of authentic compound). No **12a** was shown by ir to be present in these methanol extracts. The residue remaining after methanol extraction (0.98 g), consisting of **2a** and **3a**, was separated into the components by exhaustive extraction with four 10-ml portions of warm (40°) DMF, which removed the 1,2-isomer, leaving pure (ir[3]) **3a** in the residue. On allowing the combined DMF extracts to stand overnight at 8°, a few mg of **3a** crystallized from the solution; these were combined with the main residue, to give a total of 0.74 g (56.1%) of dried **3a**; mp > 360°. The addition of 150 ml of water to the DMF filtrate produced a precipitate of the 1,2-isomer, which, after 12 hr standing at 8°, was filtered off and dried as before, giving 0.225 g (17.0%) of pure (ir,[3] tlc) **2a**, 280° dec (lit.[1a] 270° dec). The original mother liquor, combined with the water washings, was evaporated to dryness, and the residue was recrystallized from water at temperatures not exceeding 30°, to give 0.013 g of less soluble **12b** (total yield 7.3%; product contaminated with traces of **12a** identified by tlc) and 0.24 g (17.0%) of the more readily soluble salt **5**.

In an attempt to detect the presence of salt **4** in the reaction product, a parallel experiment was performed as described above, except that the final residue resulting from evaporation of the mother liquor and water extracts was treated with 0.5 *M* aqueous NaOH to a pH of 8–9. Some insoluble **12b** was filtered off, and the aniline liberated was removed from the filtrate by evaporating the mixture to dryness (ultimately at 90° (0.05 Torr)), adding 5 ml of water and repeating the evaporation step. The crystalline residue, taken up in 20 ml of water, was acidified with 1 *M* aqueous hydrochloric acid, precipitating **7** as a white, fine-crystalline solid (0.155 g). Fractional crystallization from water produced only **7**, and no **1** was found in the precipitate, proving the absence of **4** in the water solubles.

Experiments 2–6 were conducted in an analogous fashion under the conditions listed in Table I. In experiments 2 and 3 (and, similarly, experiments 9 and 10; see below) heating was accomplished by means of the direct flame of a Bunsen burner so as to minimize heat-up time (75 sec) and maintain proper control of the reflux period, and the mixture was quenched by immersing the flask into an ice bath. Work-up in experiment 6 required some modification because of the salt-like nature of the principal product (**5**). The cooled reaction mixture was rapidly evaporated to dryness at 20° (0.05 Torr), and the residue was treated with several portions of warm (50°) water (100 ml per mmol of substrate) to dissolve all **5**. The insoluble crystalline residue, a mixture of **2a** and **3a**, was removed by filtration (not further separated in this experiment), and the filtrate on concentration at room temperature (0.1 Torr) and cooling to 8° furnished a major fraction of pure **5** and a minor one of slightly less pure **5**, bringing the total yield of this salt to 83.1%. No **4** was identified in the final fractions. In these and all subsequent experiments, fraction composiion, as well as product identity and purity, was determined by ir and, whenever feasible, by tlc.

(b) From Squaric Acid (1) and Aniline, in Methanol (Experiment 7). To the solution of 0.57 g (5 mmol) of **1** in 15 ml of methanol was added 0.93 g (10 mmol) of aniline, and the solution, from which product soon began to crystallize, was allowed to reflux for 4 hr. The solvent was distilled off at 20° (0.5 Torr), and the residue was extracted exhaustively with warm water. The water-insoluble crystalline material, 0.25 g (18.9%), constituting a mixture of **2a** and **3a**, was not separated further into the components. Work-up of the aqueous extracts as in experiment 6 furnished 0.94 g

(66.7%) of **5** and, from the final liquid concentrate, 0.05 g (3.4%) of **4**. Each salt was purified by a single recrystallization from water.

(c) From Anilinosquaric Acid (7) and Aniline in DMF (Experiments 8 and 9). In experiment 8, 0.47 g (2.5 mmol) of **7** was dissolved in 2.5 ml of DMF. After the addition of 0.23 g (2.5 mmol) of aniline, the mixture was heated for 90 min at reflux temperature and was then worked up as described for experiment 1 under (a) above. There was obtained 0.35 g (53.0%) of **3a** and 0.115 g (17.4%) of **2a**. The remainder of products, essentially **5** containing some **12b** and traces of **12a**, was not further separated.

In experiment 9, starting materials and quantities were employed as in the preceding experiment; however, the mixture was heated for only 5 min under reflux. Work-up as in experiment 1 gave 39.2% of **3a** and 13.3% of **2a** in addition to undetermined quantities of **5**.

(d) From Squaric Acid (1) and Aniline in Solvents of Varying Acidity (Experiments 13–17). The experiments are summarized in Table II, with experiment 1 reentered for comparison. Experiments 13 and 14–16 were performed as described for experiment 1 in (a) above, except that solvent mixtures were used as specified. In experiment 14 a 10% molar excess of **1** served as the acidic component. Experiment 17 was conducted by allowing the solution of the reactants in the specified concentrations to reflux for 2 hr. Solvent removal under the conventional conditions was followed by digestion of the residue with warm (50°) water. The water-insoluble material was separated into the isomer components as described for experiment 1, to furnish 29.4% of **2a** and 6.4% of **3a**. No attempts were made in these experiments to separate the salts (mainly **5**) from the water extracts.

1-Anilino-2-*p*-nitroanilinocyclobutene-3,4-dione (13a) and 1-Anilino-3-*p*-nitroanilinocyclobutenediylium 2,4-Diolate (13b). From Anilinosquaric Acid (7) and *p*-Nitroaniline in DMF (Experiment 10). *p*-Nitroaniline (0.34 g; 2.5 mmol) was added to the solution of 0.47 g (2.5 mmol) of **7** in 5 ml of DMF. The mixture was allowed to reflux for 5 min and was immediately quenched by immersing the flask in an ice bath. The fine-crystalline residue was filtered off and washed with acetone. There was thus obtained 0.071 g (9.2%) of **13b**, infusible up to 320°; mol wt 309 (by mass spectrum). The addition of water (20 ml) to the main filtrate produced a yellow precipitate, which was digested with ethanol, leaving a residue (0.010 g) of crude **13a**. The ethanol washings were evaporated to dryness, and the residue was fractionally crystallized from the same solvent, giving 0.008 g of less soluble **13a** (total yield 0.018 g, 2.3%; mp 185° dec; mol wt 309 by mass spectrum) and 0.072 g of *p*-nitroaniline. The DMF–water mother liquor, on prolonged standing at 0°, furnished a mixture of *p*-nitroaniline and **7**, from which the former was extracted with benzene. A total of 0.25 g (73%) of *p*-nitroaniline was thus recovered, as was 0.33 g (70%) of **7**.

1,2-Dipiperidinocyclobutene-3,4-dione (2b) and 1,3-Dipiperidinocyclobutenediylium 2,4-Diolate (3b). (a) From Squaric Acid (1) and Piperidine, in DMF (Experiment 11). Piperidine (0.85 g; 10 mmol) was added to the solution of 0.57 g (5 mmol) of **1** in 5 ml of DMF. The solution was allowed to reflux for 90 min. Following solvent removal at 40° (0.05 Torr), the somewhat tarry residue was chromatographed on silica gel in ethyl acetate, to give a small first fraction, from which 0.001 g (0.1%) of **2b**, mp 156–157° (from dioxane) (lit.[22] 158–160°), was isolated, and a larger second fraction, which produced 0.04 g (3.2%) of **3b**, mp 281–282° (from dioxane; lit. 281–283°;[1b,2e] 298° [2a,d]). No attempt was made to separate and identify the expected dipiperidinium squarate and other salts.

(b) From Squaric Acid (1) and Excess Piperidine (Experiment 12). In this experiment, carried out as described,[2e] 1,22 g of piperidinium chloride (10 mmol) was dissolved in 15 ml of piperidine. Following the addition of 0.57 g (5 mmol) of **1**, the mixture was heated for 10 hr at the reflux temperature. After cooling, insoluble crystalline material was filtered off and washed with 15 ml of cold water to remove admixed piperidinium chloride (1.1 g). The water-insoluble crystals of **3b** (1.16 g) were found by ir and tlc to be free from **2b**. Evaporation to dryness of the original mother liquor and thorough washing with water of the residue produced another small portion of **3b**, bringing the total yield to 1.16 g (93.6%); no **2b** was detected by tlc in the concentrated washing liquids.

Equilibration Attempts. (a) In DMF. Compound **2a**, 0.100 g, was dissolved in 10 ml of hot DMF, and the solution was heated for 1.5 hr at the reflux temperature. The crystalline solid separated upon the addition of 40 ml of water was fractionally crystallized from DMF–water. All fractions, totaling 0.095 g (95% recovery), were found by ir and tlc to constitute pure starting compound, and no **3a** was detected in the least soluble fractions. The same results were obtained on extending the heating period to 8 hr.

In a similar fashion, heating the solution of 0.100 g of **3a** in 80 ml of DMF for 1.5 hr at the reflux temperature and cooling to room temperature allowed 0.097 g (97%) of ir-pure starting compound to crystallize. The filtrate was evaporated to dryness at 50°. Ir and tlc showed no **2a** to be present in the residue, nor did this isomer appear upon extending the reflux period to 8 hr. The addition of water (1 mol per mol of dianilino compound) to the solvent in two parallel experiments produced the same results.

(b) In DMF–HCl. Compound **2a**, 0.660 g, was heated for 8 hr in a mixture of 2.5 ml of DMF and four drops of 10 *M* aqueous hydrochloric acid at the reflux temperature. Following the addition of 10 ml of DMF, the solution was allowed to cool to 110–120°. Water was then added dropwise to remaining turbidity, and product was allowed to crystallize at room temperature. The white crystalline material separated was recrystallized from DMF–water. All fractions were shown by ir and tlc to constitute pure starting compound, and no **3a** was detected in the less soluble fractions. The addition of water (40 ml) to the original mother liquor furnished another portion of pure **2a**, The filtrate, on evaporation to dryness, furnished **2a** (total recovery, 0.652 g) containing traces (tlc) of **12a** and **12b**.

Similarly, 0.660 g of **3a** was heated for 8 hr in the same solvent mixture as above at the reflux temperature. Unreacted pure starting material (0.654 g) was separated by filtration from the hot mixture. Following the addition of water (10 ml) to the filtrate, traces (<0.001 g) of **3a** crystallized slowly from the solution. The filtered liquid, on solvent removal, gave 0.001 g of yellow solid consisting of **12b**. No **2a** was detected in these final fractions.

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Registry No.—**1**, 2892-51-5; **2a**, 33512-89-9; **2b**, 29950-14-9; **3a**, 18019-52-8; **3b**, 20006-84-2; **4**, 28480-63-9; **5**, 28480-65-1; **6**, 52951-25-4; **7**, 52951-26-5; **12b**, 42131-75-9; **13a**, 52951-27-6; **13b**, 52951-29-8.

References and Notes

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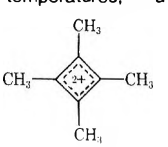
(2) (a) G. Manecke and J. Gauger, *Tetrahedron Lett.*, 3509 (1967); 1339 (1968); (b) G. Manecke and J. Gauger, *Makromol. Chem.*, **125**, 231 (1969); J. Gauger and G. Manecke, *Kinet. Mech. Polyreactions, Int. Symp. Macromol. Chem., Prepr.*, **1**, 31 (1969); (c) J. Gauger and G. Manecke, *Angew. Chem.*, **81**, 917 (1969); *Angew Chem., Int. Ed. Engl.*, **8**, 898 (1969); (d) J. Gauger and G. Manecke, *Chem. Ber.*, **103**, 3553 (1970); (e) H.-E. Sprenger, German Patent Disclosure 1618211 (1971).

(3) J. Gauger and G. Manecke, *Chem. Ber.*, **103**, 2696 (1970).

(4) Although the dicationic tetramethylcyclobutenediylium exists in SbF_5–SO_2 solution at low temperatures,[5a] a simple HMO calculation



suggests[5b] that in the tetraphenyl analog positive charge is sufficiently delocalized from the four-membered ring into the phenyl substituents to leave a net positive charge of little more than unity (1.144) on that ring. A similar situation is likely to obtain in the present case, where canonicals with δ^+ on the nitrogen atoms will contribute appreciably. Accordingly, many authors prefer,[2e,5c] or use as alternate representations,[2a-d,3] structures such as the one drawn in eq 1 as the left-hand-side canonical of **3**. Analogous mesoionic structures, with δ^+ transferred to the heterocyclic N atoms, have been proposed for 1,3-di(2-pyrryl) and similar derivatives of **1** by Treibs, *et al.*[5d,e] While we have used[6,7] the cyclobutenediylium diolate representation for reasons of simplicity and convenience of drawing, we have stressed[6a] the inadequacy of this hybrid structure. A study of the charge distribution in the two dianilino isomers **2a** and **3a** by uv and photoelectron spectroscopy is in progress in this laboratory.

(5) (a) G. A. Olah, J. M. Bollinger, and A. M. White, *J. Amer. Chem. Soc.*, **91**, 3667 (1969); (b) G. A. Olah and G. D. Mateescu, *ibid.*, **92**, 1430 (1970); (c) S. Hünig and H. Pütter, *Angew. Chem.*, **84**, 480, 483 (1972); *Angew. Chem., Int. Ed. Engl.*, 11, 431, 433 (1972); (d) A. Treibs and K. Jacob, *Justus Liebigs Ann. Chem.*, **699**, 153 (1966); **712**, 123 (1968); (e) A. Treibs, K. Jacob, and R. Tribollet, *ibid.*, **741**, 101 (1970).

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(7) B. R. Green and E. W. Neuse, *Polymer*, **14**, 230 (1973); E. W. Neuse and B. R. Green, *ibid.*, **15**, 339 (1974).
(8) Traces of **12a** were also detected (tlc) but not isolated. The formation of amides **12**, as pointed out before,[6a] does not proceed by transamidation involving **2a** or **3a** and free dimethylamine. The most likely mechanism involves an exchange reaction[9] between DMF and **7**.
(9) See, for example, J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 338.
(10) Under different conditions (8 hr in boiling butanol in the presence of catalytic amounts of 98% H_2SO_4), Gauger and Manecke[2d] observed limited (*ca.* 10%) conversion of **2a** to **3a**. This finding was interpreted, however, in terms of proton-catalyzed hydrolysis of **2a** by traces of water present in the system, followed by reamidation to **3a** by the mechanism postulated[3] for the direct formation of the 1,3-isomer from squaric acid, and therefore permits no conclusion regarding the relative thermodynamic stabilities and equlibration behavior of the two compounds.
(11) Although drawn in eq 2 as a tight ion pair, the salt **5** is probably fully solvent separated in the medium employed. The structural representation of **5** in Scheme I reflects this situation.
(12) Anilinosquarate anion, although carrying a formal negative charge of unity, is susceptible to nucleophilic attack at the carbon atoms of the four-membered ring, as this negative charge is most certainly localized on the oxygen atoms. In phenylsquarate anion, West and Powell's simple HMO calculations[13] suggest an overall charge density of +1.036 on the ring carbon atoms, with −2.097 units distributed over the three oxygen atoms.
(13) R. West and D. L. Powell, *J. Amer. Chem. Soc.*, **85**, 2577 (1963).
(14) Similar arguments hold for the related reaction type of aromatic nucleophilic displacement on activated substrates: J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1965, p 847.
(15) For the analogous phenylsquarate anion, a simple HMO calculation[13] suggests a net charge of +0.320 on C-3 as against +0.264 on each of the equivalent atoms C-2 and C-**4**.
(16) E. J. Smutny, M. C. Caserio, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 1793 (1960).
(17) Although attempts to monitor by ir spectroscopy the dissociation pattern of **7** in DMF solution failed because of the intrinsic solvent absorption in the critical carbonyl stretching region, we obtained the spectra of **7** and the salt **5** in the similarly aprotic dimethyl sulfoxide (1 *M* solutions). The acid **7** gave the two (asymmetric and symmetric) CO stretching bands at 1800 (m–s) and 1710 (s) cm^{-1} characteristic of the cyclobutene-3,4-dione system. In addition, two very weak bands due to its anion appeared at 1775 and 1655 cm^{-1}, indicating weak ionization. In the spectrum of **5**, the latter two peaks clearly predominated over the former two bands and became virtually the sole bands in this region when another mole of aniline was added, suggesting essentially complete dissociation in the more basic medium. The two-band absorption pattern of anilinosquarate anion at the positions indicated suggests that the vinylogous system is at least partially retained in the anion. The acidic H atom of the anilino group, allowing for powerful chelation and concomitant fixation of the double bond as shown in the structural representation of **5** in Scheme I, may account for this behavior.
(18) Melting points, uncorrected, taken in sealed capillaries. Ir spectra obtained on KBr pellets or DMSO solutions with a Perkin-Elmer Infracord spectrometer.
(19) Double-bond fixation in the 1-hydroxysquarate monoanion of **6**, brought about by strong H bonding to the olate oxygen atom at C-2, permits assignment of the two bands to the asymmetric and symmetric CO stretching vibrations, respectively.
(20) In C_{2v} symmetry of **1**, this vibration is an A_1 species (ν_9 in the notation of Baglin and Rose[21]). The absorption gains intensity in the (H bonded) hydroxysquarate anion of **6** owing to reduced symmetry.
(21) F. G. Baglin and C. B. Rose, *Spectrochim. Acta, Part A*, **26**, 2293 (1970).
(22) G. Maahs and P. Hegenberg, German Patent Disclosure 1518660 (1969).

The Attempted Generation of Triplet Benzyne

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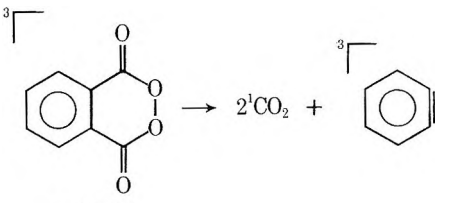
In an attempt to generate benzyne in its excited triplet state, the benzophenone-sensitized decomposition of phthaloyl peroxide (PPO) was examined. A linear Stern–Volmer diagram was obtained. Reaction with *trans*-cyclooctene gave a ratio of cycloadducts indicative of singlet benzyne.

It is generally agreed that the ground state of benzyne is a singlet.[2] Recent calculations[3] predict that the energy separation between the ground singlet and excited triplet states of benzyne may be as low as 0.72 eV.[3f] In an attempt to generate triplet benzyne we have investigated the photochemical decomposition of phthaloyl peroxide (1, PPO) from its triplet state.

Of the reported photochemical benzyne precursors[2a,4] PPO seemed best suited because of the absence of heavy atoms[5] and its solubility in organic solvents. Furthermore, Walling and Gibian have reported that photosensitized decomposition is a general process for acyl peroxides.[8] While this work was in progress, Jones and DeCamp reported that benzyne adducts with olefins can be obtained in good yield from the direct photolysis of PPO through Pyrex.[9] They concluded that the same singlet state species obtained from the thermally generated benzyne was present in the direct photolysis of PPO; they did not observe triplet state benzyne.[9]



1 (PPO)

Results and Discussion

In order to generate triplet benzyne in a photochemical reaction, the benzyne precursor should be converted into its excited triplet state. In the subsequent cleavage, triplet PPO should form benzyne in the triplet state because of the high triplet energy of carbon dioxide ($E_T > 120$ kcal/mol).[10] We have observed that PPO can be converted into its excited triplet state by sensitization with benzophenone. Quenching experiments with acrylonitrile[11] were run in acetonitrile using a merry-go-round apparatus. Analyzing for peroxide by iodometric titration[12] we found that PPO is decomposed photolytically (>330 nm) six times faster in the presence of benzophenone than in its absence. In the presence of benzophenone greater than 99% of the light is absorbed by benzophenone, supressing any direct photolysis. A Stern–Volmer plot of the inverse of the relative quantum yield ($1/\phi_{rel}$, loss of peroxide) *vs.* quencher concentration gave a straight line indicating that the decomposition of PPO proceeds *via* the excited triplet state (Figure 1).

In order to observe whether or not benzyne is actually generated, a trapping agent which has a higher triplet energy than the sensitizer is required. Furthermore, in order to be able to differentiate between singlet and triplet benzyne, it is desirable that two possible modes of reaction of

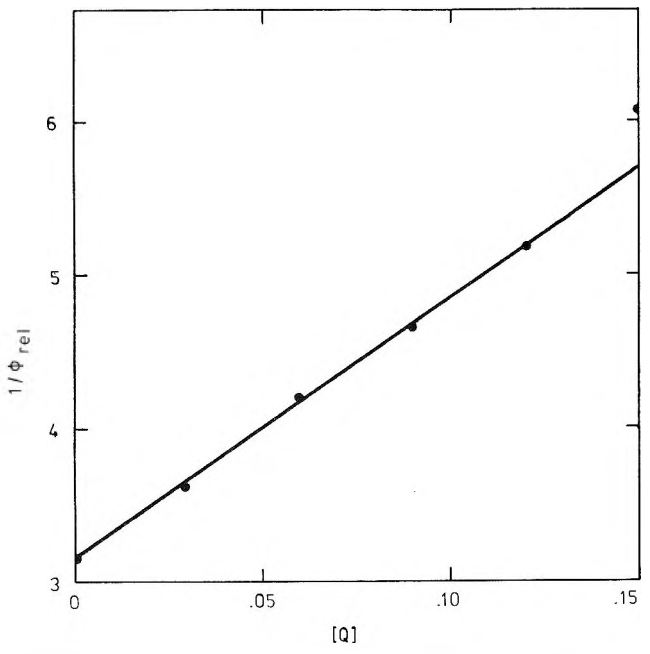
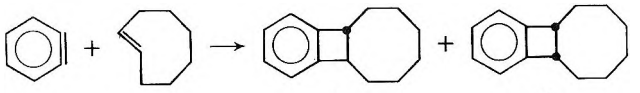


Figure 1. Stern–Volmer plot of $1/\phi_{rel}$ *vs.* the concentration of acrylonitrile [Q].

benzyne with the trapping agent exist. Whereas identical product ratios obtained from benzyne generated in different ways would suggest a common intermediate, different product ratios would suggest that the benzyne intermediates are different. Gassman and Benecke[13] have observed that when benzyne generated from benzenediazonium-2-carboxylate reacts with *trans*-cyclooctene, *trans*-**2** and *cis*-**3** [2 + 2] cycloaddition products are formed (45 and 13% yield, respectively) in a nonconcerted reaction.

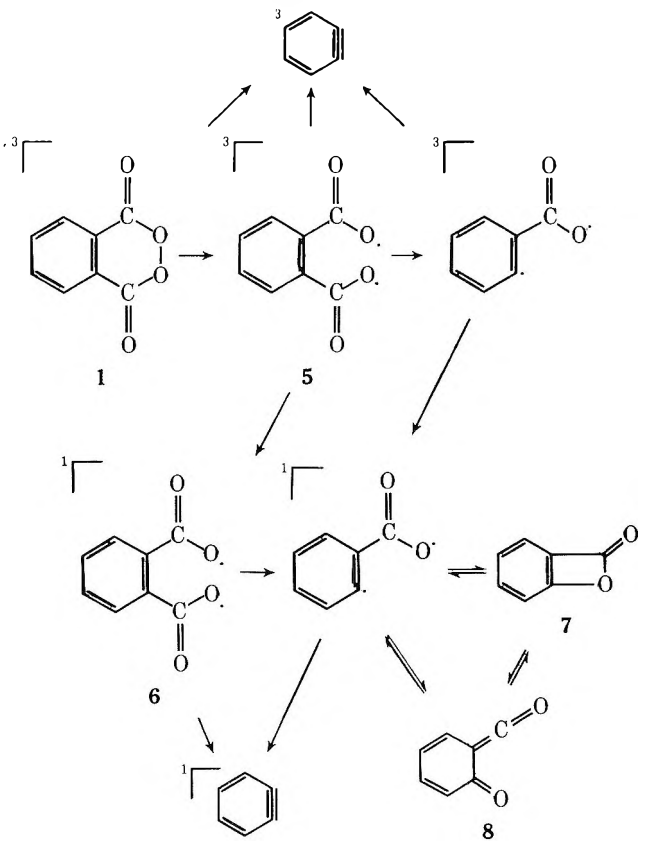


2 **3**

Using *trans*-cyclooctene as a trapping agent we would expect that the 1,4 diradical intermediate[13] formed in the cycloaddition with triplet benzyne would have a longer lifetime than in the reaction with singlet benzyne. In the triplet reaction a spin inversion is necessary before rebonding can occur to form the cycloadduct. Hence there is more time for rotation to the more stable cis conformation to occur before rebonding takes place. It is therefore reasonable to expect an increase in the ratio of cis to trans cycloadducts relative to the ratio observed by Gassman, if a triplet state intermediate is involved (Skell's postulate).[14]

When *trans*-cyclooctene was used to trap the benzyne from the benzophenone-sensitized decomposition of PPO, the results were complicated by the observation that PPO and *trans*-cyclooctene react thermally at room temperature,[15] forming phthalic anhydride as the main product and cyclooctene oxide, neither of which forms **2** or **3**. In order to suppress this thermal reaction a solution of PPO and *trans*-cyclooctene in acetone[17] prepared at room temperature was subjected to benzophenone-sensitized photolysis at −60°. Gas chromatographic analysis of the reaction mixture still showed mainly the products of the thermal reaction, but also revealed the low yield formation of the two cycloadducts **2** and **3** in the ratio 82:18, respectively.[18] These cycloadducts were formed in the same ratio observed in the reaction of thermally (65°) generated (from benzenediazonium-2-carboxylate) singlet benzyne and *trans*-cyclooctene (81:19 for **2** and **3** respectively). More significantly singlet benzyne generated at −60° under the same

Scheme I[21]



conditions by direct irradiation (>330 nm) of benzothiadiazole 1,1-dioxide[19] led again to **2** and **3** in a 82:18 ratio. This result suggests that a reaction of singlet benzyne was observed in the photosensitized decomposition of PPO.[20]

The possible stages in the decomposition of triplet PPO including spin inversion and demotion to the ground singlet states are shown in Scheme I. The present results suggest that the rate of triplet–singlet interconversion in one of the intermediates is faster than the loss of two carbon dioxide molecules which results in benzyne. It seems most reasonable that this spin inversion takes place in intermediate **5**. The spin density in this diradical should be mostly localized on the electronegative oxygen atoms which are separated from one another by four carbon atoms. Hence, in this species one might expect the energy difference between the singlet and triplet manifolds to be small, and that the spin inversion would therefore be rapid. We expect that this situation would arise with any sensitized reaction in which benzyne is generated in a stepwise process. Future attempts at the synthesis of triplet benzyne are therefore likely to be successful only if a one-step decomposition of the triplet precursor can be realized.

Experimental Section

Reagents. Phthaloyl peroxide (PPO) was prepared according to Jones[9] or Russel[24] and contained 94% active oxygen by iodometric titration.[25] Benzothiadiazole 1,1-dioxide was purified *via* its dihydro compound.[19] Benzophenone was recrystallized from ethanol. Acetonitrile and acrylonitrile were freshly distilled.

***trans*-Cyclooctene.** trans-Cyclooctane-1,2-diol[26] (101 g, 0.70 mol) and ethyl orthoformate (104 g, 0.70 mol) were heated at 140–160° for 8 hr, while ethanol distilled off. Fractionation of the mixture yielded after a forerun 68.8 g (34%) 2-ethoxy-*trans*-cycloocta-no[1,2-*d*]dioxolane.

This as well as the polymeric pot residue can be cleaved to *trans*-cyclooctene (*cf.* ref 27); 20.3 g of the above dioxolane was heated at 220–240°. A stream of nitrogen swept the products into a cooled receiver. The condensate (13.7 g) was fractionated. The fraction of bp 78° (72 Torr) was taken up in petroleum ether (40–

60°), washed twice with water, and with brine, dried (Na_2SO_4), and distilled giving cyclooctene (95.5% trans, 4.5% cis by vpc).

Photolysis. PPO (60.0 mg) and benzophenone (60.0 mg) were dissolved in 10 ml of acetonitrile in a 10 mm o.d. Duran tube. After degassing by four freeze–thaw cycles the tube was sealed and irradiated in a merry-go-round apparatus by a high-pressure mercury arc (Hanau-Q-700) *via* 1.5 cm of a filter solution[28] containing 650 g of $NaBr{\cdot}2H_2O$ and 3.00 g of $Pb(NO_3)_2$ per liter (cut-off 330 nm). The filter system was chosen such that after 20-min irradiation 46% of PPO had been destroyed in the presence of benzophenone and <8% in the absence of benzophenone. Samples were analyzed iodometrically.[25] One sample was irradiated for 5 hr and the tube was frozen, opened, and connected to a system which swept the carbon dioxide formed into $Ba(OH)_2$ solution with nitrogen. Titration with 0.1 *N* HCl showed 73% of 2 equiv of CO_2 to be formed. The residual solution gave a negative test for peroxide.

Quenching Study. Photolyses were carried out as above (20-min irradiation). The samples contained 0.02–0.10 ml of acrylonitrile. Relative quantum yields were determined iodometrically.[25] With higher acrylonitrile content (up to 0.5 ml) total quenching was approached.

Benzyne Trapping. PPO (60.0 mg) and benzophenone (60.0 mg) were dissolved in 10 ml of acetone in a 10-mm o.d. Solidex tube. *trans*-Cyclooctene (0.255 ml) was added and the mixture was immediately degassed by three freeze–thaw cycles. The cold tube was positioned in a Liebig condenser, through the jacket of which methanol at −50 to −60° was circulated, and irradiated for 5 hr as above. After stripping the solvent, the reaction mixture was analyzed by vpc (⅛ in. × 6 ft column with 10% Apiezon on 60/80 Chromosorb R, 180°, 35 ml of N_2/min; or ¼ in. × 12 ft column with 15% polyphenyl ether OS 124 on 60/100 kieselgur, 180°, 80 ml of N_2/min). The main component was phthalic anhydride. Two minor peaks (ratio 82:18) had the same retention time as **2** and **3** prepared by the method of Gassman.[13] In our hands the latter method gave **2** and **3** in a 81:19 ratio. For final identification the sample was chromatographed on a 4 m × 3 mm glass column with 2.5% SE 52 on 80/100, Chromosorb G-AW DMCS, 160°, 25 ml of He/min. The column effluents were transferred *via* on all-glass two-stage Biemann separator to an Atlas CH4B mass spectrometer. **2** and **3** from the PPO reaction showed the same retention times and mass spectra as the authentic samples.

Photolysis of Benzothiadiazole 1,1-Dioxide. Benzothiadiazole 1,1-dioxide (9.36 mmol) in 10.0 ml of acetone (−10°) was added to *trans*-cyclooctene (0.255 ml) at −78°. After degassing, the mixture was photolyzed as above. Although decolorized after 20 min, the irradiation was continued for 4 hr. Vpc analysis (⅛ in. × 12 ft column with 4% SE 52 on Chromosorb G, 135°, 50 ml of N_2/min) showed the presence of **2** and **3** in a 82:18 ratio.

Photoisomerization of *trans*-Cyclooctene. Benzophenone (60.0 mg) and *trans*-cyclooctene (0.255 ml) were photolyzed exactly as above. Vpc analysis (300 ft × 0.01 in. capillary column with Carbowax 20M, 70°, 40 psi He) showed that 7.3% *cis*-cyclooctene had been formed.

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Registry No.—**1**, 4733-52-2; benzyne, 462-80-6; *trans*-cyclooctene, 931-89-5; *trans*-cyclooctane-1,2-diol, 42565-22-0; benzophenone, 119-61-9; benzothiadiazole 1,1-dioxide, 37150-27-9; ethyl orthoformate, 122-51-0.

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Configuration and Conformation of *cis*- and *trans*-3,5-Dimethylvalerolactones[1]

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The synthesis and resolution of 3-methyl-5-oxohexanoic acid (**5**) are presented. A synthesis of (*S*)-**5** from (4*R*)-4-methyl-6-oxoheptanoic acid is also reported. The different isomers of **5** were used to prepare all four optical isomers, as well as the two racemic pairs of *cis*- and *trans*-3,5-dimethylvalerolactones. The synthetic routes used established the configuration of these lactones at position 3. The configuration at position 5 and the conformational assignment of these lactones were established by an analysis of the ^{1}H nmr, ^{13}C nmr, and CD spectra.

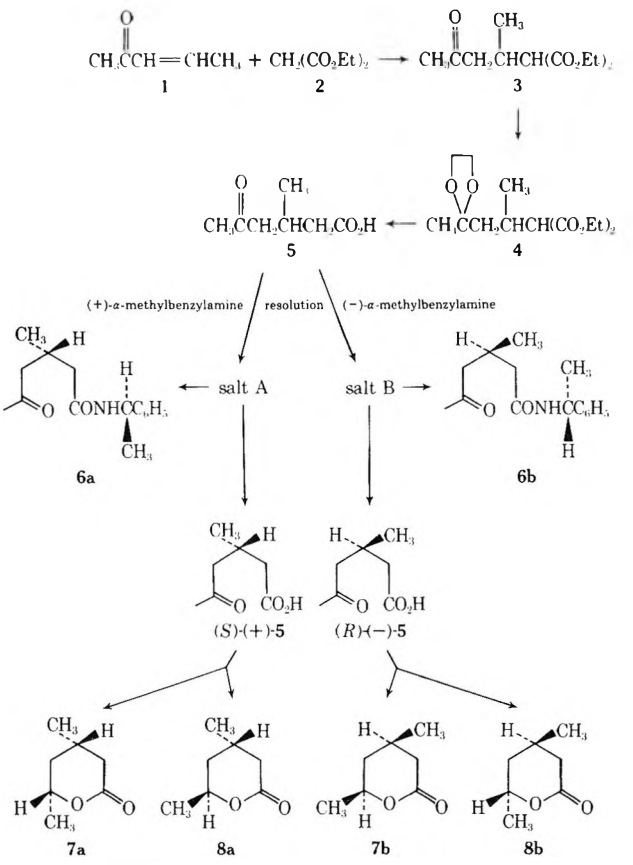
Studies concerning the structure, configuration, and conformation of saturated δ-lactones are a subject of continuing interest. X-Ray analyses of lactones have shown that the carbonyl, the ethereal oxygen, and the two adjacent carbon atoms lie in the same plane.[2] The lactone ring can, therefore, assume either a half-chair or a boat conformation, and both conformations have been found in the crystalline state. In addition, infrared (ir),[2c] ultraviolet (uv),[3] optical rotatory dispersion (ORD), and circular dichroism (CD)[4] and proton nuclear magnetic resonance (^{1}H nmr)[5] studies have been used to study the structure, configuration, and conformation of saturated lactones in solution. The results have shown that some δ-lactones exist in a half-chair conformation in solution, whereas other δ-lactones possess a boat conformation.

The present paper contains the synthesis and analysis by various ^{1}H nmr, ^{13}C nmr, and CD techniques of the configuration and conformation of 3,5-dimethylvalerolactones.[6]

Results and Discussion

Synthesis. The synthesis of all four optical isomers of 3,5-dimethylvalerolactone was accomplished as shown in Chart I. Diethyl 1-methyl-3-oxobutylmalonate (**3**) obtained by the Michael addition of diethyl malonate (**2**) to 3-penten-2-one (**1**) was converted to its ethylene ketal derivative (**4**). Alkaline hydrolysis of **4**, followed by acidification and thermal decarboxylation, yielded (*RS*)-3-methyl-5-oxohexanoic acid (**5**).[7] Attempts to prepare **5** directly from **3** without protection of the 3-oxo function gave very low yields of **5**. We found that *d*-(+)- and *l*-(−)-α-methylbenzylamine effected a high yield optical resolution of **5** to give (*S*)-(+)-**5** and (*R*)-(−)-**5**, respectively. When the salts A and B were treated with *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ)[8] in tetrahydrofuran, the diastereomeric amides **6a** and **6b** were obtained in high yield. These products could be used to determine the optical purity of the resolved acids. The nmr spectra of **6a** and **6b** as well as the racemic amide obtained from (*RS*)-**5** and (−)-α-methylbenzylamine showed only one methyl resonance for the CH_3CO and $NCHCH_3$ moieties. However, the nmr spectra of the amide from (*RS*)-**5** obtained in the presence of tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium [Eu(fod)$_3$] showed two singlets for the CH_3CO group and two doublets for the $NCHCH_3$ group. From the integrated intensities of the CH_3CO and $NCHCH_3$ signals(s) of **6a** and **6b** it was possible to assay for their optical purity. These results established that the amides **6a** and **6b** were >95% optically pure, and, thus, the acids (*S*)-(+)-**5** and (R)-(−)-**5** possess similar optical purities (see Experimental Section for details).[9] Reduction of (*S*)-(+)-**5** with sodium borohydride in ethanol or catalytically in the presence of platinum oxide gives a mixture of *cis*-(3*S*,5*R*)- and *trans*-(3*S*,5*S*)-3,5-dimethylvalerolactones **7a** and **8a**, respectively. Reduction of (*R*)-(−)-**5** in a similar manner gives a mixture of the optical isomers **7b** and **8b**, whereas reduction of (*RS*)-**5** gives a mixture of (3*RS*,5*SR*)-*cis*- and (3*RS*,5*RS*)-*trans*-3,5-dimethylvalerolactones **7** and **8**, respectively.

Chart I



It was not possible to separate the cis and trans lactones by distillation or liquid chromatography. However, the amides obtained on treating the mixture of lactones with pyrollidine could be separated by chromatography on aluminum oxide. The lactones could be regenerated by treating the separated pyrollidinamides with ethanolic sodium hydroxide. Regeneration of the lactones from the separated pyrollidinamides under acidic conditions gave a mixture of cis and trans lactones.

(3*S*)-3-Methyl-5-oxohexanoic acid (**5**) could also be obtained from (4*R*)-4-methyl-6-oxoheptanoic acid (**9**)[10] by the route shown in Chart II. Esterification of **9** followed by treatment with ethylene glycol in refluxing benzene containing *p*-toluenesulfonic acid gave (4*R*)-methyl 4-methyl-6-ethylenedioxyheptanoate (**10**). Addition of phenylmag-

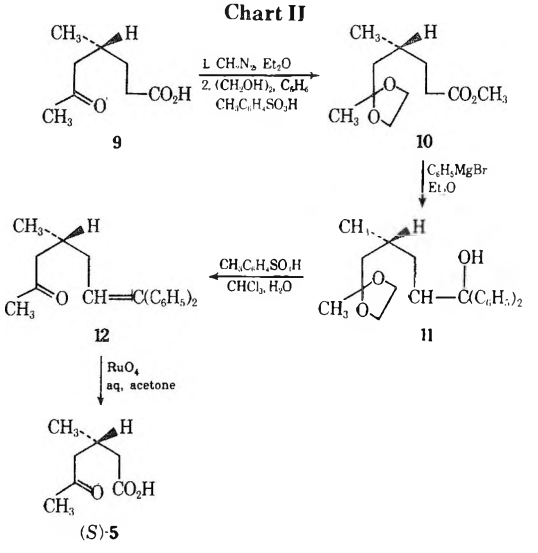
Table I
Proton Chemical Shifts of *cis*- and *trans*-3,5-Dimethylvalerolactones[a]

Compd	Solvent	C-3 CH_3[b]	J_{H,CH_3}[c]	$\Delta_{C_6D_6}^{CDCl_3}$[d]	C-5 CH_3[b]	J_{H,CH_3}[e]	$\Delta_{C_6D_6}^{CDCl_3}$	C-5 H[b]	bw[f]	$\Delta_{C_6D_6}^{CDCl_3}$
7	CCl_4	1.01 (d)	5.7		1.33 (d)	6.0		4.29 (m)	42	
	$CDCl_3$	1.01 (d)	5.5		1.36 (d)	6.2		4.40 (m)	40	
	C_6D_6	0.63 (d)	5.9	+0.38	1.09 (d)	6.2	+0.27	3.86 (m)	36	+0.54
8	CCl_4	1.09 (d)	6.1		1.33 (d)	6.1		4.46 (m)	37	
	$CDCl_3$	1.09 (d)	6.1		1.36 (d)	6.2		4.56 (m)	35	
	C_6D_6	0.66 (d)	6.2	+0.43	1.07 (d)	6.2	+0.29	4.05 (m)	39	+0.51

[a] Spectra obtained on a Varian HA-100 spectrometer. Chemical shifts given in δ values relative to $SiMe_4$. [b] d = doublet, m = multiplet. [c] Coupling constant with C-3 H. [d] $\Delta_{C_6D_6}^{CDCl_3}$ = difference between chemical shift in $CDCl_3$ and C_6D_6. [e] Coupling constant with C-5 H. [f] Band width of H-5.

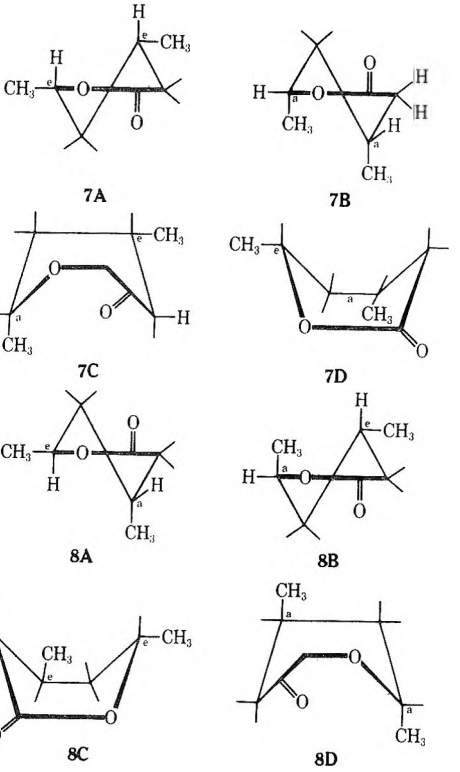
nesium bromide to **10** gave (4*R*)-1,1-diphenyl-4-methyl-6-ethylenedioxyheptanol (**11**). Treatment of **11** with a refluxing solution of *p*-toluenesulfonic acid in chloroform effected both elimination of water and deketalization to give (4*R*)-7,7-diphenyl-4-methyl-2-oxoheptene (**12**). Compound **12** was subjected to ruthenium tetroxide oxidation to give (3*S*)-3-methyl-5-oxohexanoic acid (**5**).

Chart II



Stereochemistry. *cis*- and *trans*-3,5-dimethylvalerolactones **7** and **8**, respectively, can each exist in two possible half-chair and two possible boat conformations (A, B, C, and D). Ir studies have demonstrated that δ-lactones that have half-chair conformations show carbonyl stretching frequency in the range 1730–1750 cm^{-1} and δ-lactones that possess boat conformations show absorption in the range 1758–1765 cm^{-1}.[2c] Since both lactones **7** and **8** show infrared carbonyl absorption (CCl_4) at 1736 cm^{-1}, it can be assumed that both **7** and **8** possess half-chair conformations. Inspection of Drieding models shows that the cis isomer has the C-3 CH_3 and C-5 CH_3 groups in a cis 1,3 relationship and would be expected to exist preferentially in conformation **7A** which avoids diaxial opposition of these groups.[11] In addition, since the low- and high-temperature nmr analyses of both **7** and **8** show no new signals and show no line broadening of the signals present in the 180 to −80° temperature range, conformational homogeneity is indicated for both lactones. Thus, the problem is to determine which of the two lactones has the cis structure and to choose between the two possible half-chair conformations for the trans isomer. A detailed analysis of the ^1H nmr, ^{13}C nmr, and CD properties of **7** and **8** was used to accomplish these assignments.

Proton Nmr. The proton nmr data for lactones **7** and **8** in three solvents are listed in Table I. Concentrating first on the spectra obtained in CCl_4, the significant aspects are the shifts in the two spectra of the C-3 CH_3 (δ 1.01–1.09) and C-5 H (δ 4.29–4.46) and the appearance of the C-5 CH_3 group at δ 1.33 in both spectra. These results can be explained if the nmr spectrum having the highest field resonance for the C-3 CH_3 is assigned to the cis isomer which for reasons already stated exists preferentially in conformation **7A**. Since the cis and trans isomers have the same



resonance for the C-5 CH_3 group (δ 1.33), the trans isomer seems best represented by conformation **8A** which has this group in an equatorial position. Johnson, *et al.*,[12] have found that equatorial methyl groups on cyclohexanone appear at higher field and have J_{vic} coupling constants smaller than axial methyl groups; thus the shift of δ 1.01–1.09 ppm and the increased J_{vic} for the C-3 CH_3 group in going from **7** and **8** (equatorial to axial CH_3 group) are the results expected. In addition, the 0.17-ppm (δ 4.29–4.46 ppm) downfield shift of the C-5 H in going from **7** to **8** can be explained by the cis 1,3-diaxial interaction of the C-3 CH_3 and C-5 H of **8** which is absent in **7**. Deshielding in the order of 0.18 ppm has been observed in cyclohexanols in going from 1,3-H–H to 1,3-CH_3–H interactions.[13]

The correctness of the conformations **7A** and **8A** assigned to the cis and trans lactones, respectively, is further supported by measurements of the solvent effect (Table I). The solvent shifts $\Delta_{C_6D_6}^{CDCl_3}$ measured for the C-5 CH_3 and the C-5 H in lactones **7** and **8** show no significant differences. These results indicate that both lactones **7** and **8**

Table II
Nmr Spectral Data of *cis*- and *trans*-3,5-Dimethylvalerolactones 7 and 8 in the Presence of Eu(dpm)$_3$[a]

Compd	Medium	C-3 CH_3[b]	J_{H,CH_3}[c]	C-5 CH_3[b]	J_{H,CH_3}[e]	C-5 H[b]	bw[f]	C-2 H_{ax}	$J_{2ax,2eq}$	$J_{2ax,3ax}$	$J_{2ax,5eq}$	C-2 H_{eq}[g]	$J_{2eq,3ax}$	$J_{2eq,4eq}$	$J_{2eq,3eq}$
7	CCl_4 + 0.23 mol equiv of Eu(dpm)$_3$	1.27 d)	6.5	1.74 (d)	6.1	5.07	37	3.28 (q)	17.3	10.3		3.98 (o)	5.8	1.9	
	$CDCl_3$ + 0.24 mol equiv of Eu(dpm)$_3$	1.17 (d)	6.3	1.60	6.3	4.83 (m)	40	2.78 (q)	17.3	10.4		3.46 (o)	5.5	1.8	
8	CCl_4 + 0.24 mol equiv of Eu(dpm)$_3$	1.50 (d)	6.5	1.95 (d)	6.3	5.49	38	3.88 (q)	16.1		9.0	4.39 (q)			5.6
	$CDCl_3$ + 0.38 mol equiv of Eu(dpm)$_3$	1.27 (d)	6.3	1.61 (d)	6.1	4.96 (m)	37	2.87 (q)	16.5		9.0	3.33 (q)			5.5

[a–f] See Table I for explanation of footnotes. [g] o = octet.

form collision complexes with approximately the same geometry. Moreover, the $\Delta_{C_6D_6}^{CDCl_3}$ values of +0.27 and +0.29 for the C-5 CH_3 of 7 and 8, respectively, are close to the +0.22 to +0.28 values found for similarly situated equatorial C-5 CH_3 groups in several δ-lactones and are quite different from the +0.36 to +0.39 values found for similar axial CH_3 groups.[5a] The $\Delta_{C_6D_6}^{CDCl_3}$ values for the C-3 CH_3 in 7 and 8 are +0.38 and +0.43 ppm, respectively. According to the suggested assignments the C-3 CH_3 group is equatorial in 7 and axial in 8. The axial CH_3 group of 8 shows a larger upfield shift as expected. However, the difference is smaller than might be anticipated. These results suggest that the trans isomer 8 may actually exist as a slightly flattened half-chair form of **8A**.

The application of shift reagents enabled us to obtain additional support for the correctness of the assignments **7A** and **8A** for *cis*- and *trans*-3,5-dimethylvalerolactones. The addition of Eu(dpm)$_3$ to a CCl_4 solution of 7 and 8 shifted the C-2 methylene group into a spectral region where the geminal spin–spin splitting of the C-2 H's and its splitting with the C-3 H becomes amenable to first-order analysis.[14] Both compounds 7 and 8 exhibit a rather large geminal coupling constant $J_{2ax,2eq}$ = 17.3 and 16.1 Hz, respectively.[15] Since the C-2 H protons are attached to an sp^3 carbon, the large J_{gem} values must be due to an enhanced $\sigma^- - \pi$ interaction with the adjacent lactone carbonyl. Such large values for J_{gem} can be accounted for according to Barfield and Grant,[16] if the carbonyl group bisects the methylene group. This stereochemistry in combination with a planar lactone grouping necessitates that the cis and trans lactones exist in the half-chair conformation **7A** and **8A**. In the case of 7 the vicinal coupling $J_{2ax,3ax}$ = 10.3, $J_{2eq,3ax}$ = 5.8, and the long-range coupling of 1.9 Hz observed between C-2 H_{eq} and C-4 H_{eq} in **7A** are also in accord with this assignment. The large long-range coupling between C-2 H_{eq} and C-4 H_{eq} is particularly revealing since the geometry in the half-chair conformation **7A** has these protons in the planar W configuration necessary for maximum effect.[17] The geometry of a boat or half-boat conformation for the cis isomer is not favorable for the observation of such a large long-range $J_{2eq,4eq}$ coupling. In the case of the trans isomer the slightly lower J_{gem} value (16.1 Hz), the slightly larger J_{vic} (9.0 and 5.6 Hz) than expected, and the absence of C-2 H_{eq} and C-4 H_{eq} long-range coupling support the earlier suggestion based on solvent shift studies that the trans lactone **8A** has a slightly flattened half-chair conformation.[18]

Lambert has shown that the geometry about CH_2–CH_2 fragments and certain substituted ethylene fragments in many cyclic six-membered rings can be defined by a ratio of the two coupling constants J_{trans} and J_{cis}.[19] The ratio J_{trans}/J_{cis} which is called an R value will remain constant in similar systems even though J_{trans} and J_{cis} are variable and thus are dependent only on the geometry about the fragment. Since the R-value method has been used to determine the geometry of the X–CH_2CHR–Y segment of several other six-membered rings, we have applied it to the lactones 7 and 8. The R values calculated from the data in Table II for the CH_2CHCH_3 fragment C-2–C-3 for lactones 7 and 8 are 1.78 and 0.62, respectively. These results show that the C-2–C-3 fragment geometry is different in the two lactones. Thus, if the cis lactone 7 has the conformation **7A** as the steric requirements and ir data indicate, the trans lactone 8 must have the conformation **8A** or **8D** to be consistent with the calculated R values. The latter is inconsistent with the ir data and also seems unlikely for steric reasons. The unusually small R value for the C-2–C-3 fragment of 8 would be compatible with the proposal that **8A** actually exists in a slightly flattened half-chair conformation.

Carbon-13 Nmr. Carbon-13 (^{13}C nmr) chemical shifts are remarkably sensitive to molecular geometry, and consequently ^{13}C nmr studies can be useful for stereochemical and conformational elucidation.[20] From fundamental studies on cyclohexanes[21] and the related investigation of cyclohexanones[22] it was found that, other things being equal, an axial methyl carbon on the ring is more shielded than an equatorial methyl carbon by about 4 ppm. The carbons that are γ to the methyl group (3 and 5 in methylcyclohexane) are also shifted upfield. This effect has been referred to as the γ effect. In addition, equatorial methyl groups impart deshielding α and β effects of about 6 and 9 ppm, respectively, while axial methyl functions exert similar α and β effects of about 1 and 5 ppm, respectively.[23]

The ^{13}C nmr chemical shifts relative to tetramethylsilane for *cis*- and *trans*-3,5-dimethylvalerolactones 7 and 8, respectively, are listed in Table III. The ^{13}C nmr chemical-shift assignments are based on single frequency off-resonance decoupling (SFORD) experiments and empirical correlations[20,23] including direct comparison to the ^{13}C nmr chemical-shift assignments of *cis*- and *trans*-3,5-dimethylcyclohexanones which are also listed in Table II.[22] The ^{13}C nmr chemical-shift values are in accord with the conformations **7A** and **8A**. The C-5 CH_3 is equatorial in both **7A** and **8A**, and, thus, the ^{13}C nmr chemical shifts of the C-5 CH_3 in both lactones are almost identical. The difference of +2.94 ppm between the equatorial and axial C-3 CH_3 carbon of **7A** and **8A** respectively, results from a steric effect of the C-3 CH_3 of **8A** with C-5 (γ carbon) and its axial hydrogen. The substantial upfield shift (+3.38 ppm) at C-5 (γ

Table III
Carbon-13 Chemical Shifts of *cis*- and *trans*-3,5-Dimethylvalerolactones in C_6D_6[a]

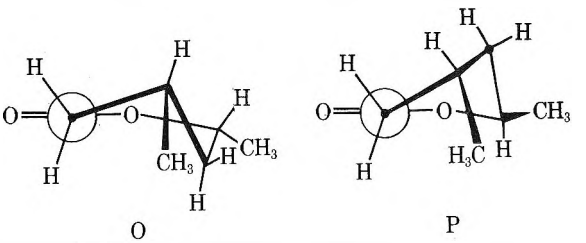
Compound	Solvent	Chemical shifts, ppm[b] C-1	C-2	C-3	C-4	C-5	C-3 CH_3	C-5 CH_3
cis-3,5-Dimethylvalerolactone (**7**)	C_6D_6	169.75 (s)	37.92 (t)	21.80 (d)	38.65 (t)	75.89 (d)	26.75 (q)	21.40 (q)
trans-3,5-Dimethylvalerolactone (**8**)	C_6D_6	170.62 (s)	36.60 (t)	21.31 (d)	37.43 (t)	72.51 (d)	23.81 (q)	21.16 (q)
cis-3,5-Dimethylcyclohexanone[c,d]		208.2	49.4	33.4	43.0	33.4	22.6	
trans-3,5-Dimethylcyclohexanone[c,d]		208.6	48.8	29.8	39.9	29.8	21.1	

[a] Chemical shifts are in parts per million relative to internal tetramethylsilane. [b] Signal multiplicity obtained from single frequency off-resonance experiments is given in parentheses beside the chemical-shift value; s = singlet, d = doublet, t = triplet, q = quartet. [c] Taken from ref 22. [d] Original data converted $\delta(TMS) = \delta(CS_2) + 192.8$.

to the C-3 CH_3) of the δ-lactone **8A** with an axial C-3 CH_3 as compared with **7** with an equatorial C-3 CH_3 can be ascribed to the same steric effect (γ effect). In the case of *cis*- and *trans*-3,5-dimethylcyclohexanone shifts of 1.5 and 3.6 ppm were observed for the C-3 CH_3 (C-5 CH_3) and C-5 (C-3) carbon in going from the cis to the trans isomer.[22] The difference in chemical shift between the carbonyl carbons in **7A** and **8A** as well as those in the *cis*- and *trans*-3,5-dimethylcyclohexanones is small. The relative insensitivity of the ^{13}C resonance of this carbon to substituent effects has been attributed to the lack of directly bonded protons which make the normal mechanism of long-range substituted effects inoperative.[22] The ^{13}C nmr resonances of C-2 and C-4 of **7A** appear at lower field relative to the same resonances in **8A**. These results are expected since the equatorial C-3 CH_3 of **7A** would impose a greater deshielding (β effect) than the axial C-3 CH_3 of **8**. Similar results are observed with the 3,5-dimethylcyclohexanones.[22] The ^{13}C nmr chemical shifts of C_3 in both **7A** and **8A** are approximately the same. Everything else being equal, the C-3 of **7A** which has an equatorial CH_3 substituent should be deshielded relative to **8A** which has an axial substituent (α effect). Apparently the deshielding α effect of the equatorial CH_3 group of **7A** is balanced by a larger γ effect from the ethereal oxygen of **7A**. If **8A** actually exists in a flattened half-chair conformation as previously suggested and if the dihedral angle between bonds C-1–O and C-2–C-3 is larger than the same angle in **7A**, **7A** would be expected to show a larger γ effect.[24]

CD Spectra. Several empirical rules have been proposed to explain the relation between the sign of the n–π* Cotton effect (CE) of optically active lactones and their absolute configuration. Klyne and coworkers[25] formulated a sector rule, and Snatzke and coworkers[26] used a system with curved nodal surfaces; however, neither of these methods is applicable to lactones that contain a second chiral sphere.[27] Wolf,[28] Beecham,[29] and Legrand and Bucourt[30] have related the sign of the Cotton effects of δ-lactones to the chiral character of the lactone ring. Legrand and Bucourt rules on ring chirality allow the sign of a CE to be predicted for conformations other than half-chair and boat forms.[27] According to the rules of these authors the sign of the n–π* band of nonplanar lactones is opposite to the sign of the torsion angle between bonds C-1–O and C-2–C-3 when a Newman projection is viewed along bond C-2–C-1.[31] The CD spectra of both **7aA** and **8aA** show negative CE for the lactone n–π* transition. Lactone **7aA** shows a negative minimum at 225 nm ($[\theta] = -1760$) and lactone **8aA** shows a negative minimum at lower wavelength (214 nm) but with larger molecular ellipticity ($[\theta] = -5169$).

The Newman projections O and P of **7aA** and **8aA**, respectively, show lactone **7** in the half-chair conformation O and lactone **8A** in a conformation P where the torsion angle is approximately +20°. The conformation P, which is intermediate between a half-chair and boat conformation, predicts a −CE for lactone **8aA**. In addition, this conformation, which has a larger torsion angle than O could account for the larger CE minimum of lactone **8**. The −CE of lactone **8** could also be accounted for by the half-chair conformation (**8B**) or the half-boat conformation (**8C**). However, the chair form **8B** does not account for the 12-nm difference[32] in the CD minimum of **7A** and **8A**, the boat form **8C** does not account for its ir carbonyl absorption at 1736 cm^{-1}, and neither **8B** nor **8C** is consistent with the ^1H and ^{13}C nmr data.



O P

Conclusions

The synthesis of all four optical isomers of 3,5-dimethylvalerolactone has been achieved. This was accomplished by first resolving (±)-**5**- into (*S*)-(+)- and (*R*)-(−)-3-methyl-5-oxohexanoic acid (**5**), followed by reduction of the 5-keto group of **5**, lactonization of the 5-hydroxy-3-methylhexanoic acids formed, and separation of the resulting cis and trans lactones in each case. Since the optical isomers of the methyl ester of (*R*)-**5** have been related to (*R*)-(+)-3-methylhexanoic acid,[33–35] their configuration, as well as those at the 3 position of the 3,5-dimethylvalerolactones, is established. (*S*)-(+)-**5** was also prepared from (4*R*)-4-methyl-6-oxoheptanoic acid (**9**) whose absolute configuration has been determined.[36,37] The absolute stereochemical assignment at the 5 position of these lactones, and, thus, the complete stereochemical assignment of the four 3,5-dimethylvalerolactone enantiomers was established by a detailed analysis of their ^1H nmr, ^{13}C nmr, and CD spectra. In addition, the cis and trans lactones **7** and **8**, resectively, were shown to possess the half-chair conformations **7A** and **8A**, respectively. In the case of **8** the data indicate **8** to have actually a slightly flattened form of the half-chair **8A**.

Experimental Section

General. Melting points were determined on a Kofler hot stage microscope using a calibrated thermometer. Ir spectra were measured with a Perkin-Elmer Model 467 grating infrared spectrophotometer. Uv absorption spectra were obtained on a Cary Model 14 spectrometer. The purity of the compounds was checked by glc analyses using a Hewlett Packard Model 700 gas chromatograph

equipped with a thermal conductivity detector. Stainless steel columns (6 ft × ⅛ in.) packed with 10% SE-30 (column A) or 10% DEGS (column B) on 40–60 mesh Chromosorb W (AWS) were used. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

Nmr Spectra. Proton nmr spectra were recorded on a Varian Model HA-100 spectrometer using tetramethylsilane (TMS) as an internal standard. The high- and low-temperature studies were conducted at North Carolina State University at Raleigh, N.C., on a Varian HA-100 spectrometer.[38] Nitrobenzene was used as solvent for the high-temperature studies (up to 180°) and trichlorofluoromethane was used as solvent for the low-temperature studies (−85° to ambient temperature).

The ^{13}C nmr spectra were determined at 24.92 MHz on a modified JEOL JNM-PS-100 FT-NMR interfaced with a Nicolet 1085 Fourier transform computer system. Spectra were obtained in benzene-d_6 (C_6D_6) in a 10-mm tube. The spectra were recorded at ambient temperature by using the deuterium resonance of C_6D_6 as the internal lock signal. All proton lines were decoupled by a broad band (~2500 Hz) irradiation from an incoherent 99.076-MHz source. Interferograms were stored in 8K of computer memory (4K output data points in the transformed phase corrected real spectrum), and chemical shifts were measured on 5000-Hz sweep width spectra. Typical pulse widths were 10.0 μsec, and the delay time between pulses was fixed at 1.0 sec. Normally 1012 (twice as many for single frequence off-resonance experiments) data accumulations were obtained on a 100 mg/2 ml of solvent sample. The chemical shifts reported are believed accurate to within ±0.05 ppm.

CD Spectra and Optical Rotations. CD measurements were made at ambient temperatures (~25°) with a Durrum-Jasco Model-20 ORD–CD spectropolarimeter calibrated with *d*-10-camphorsulfonic acid (0.313° ellipticity for a 1 mg/ml solution in water using a 1.0-cm cell at 290.5 nm). All observed rotations at the sodium D line were determined with a Perkin-Elmer Model 141 polarimeter (1-dm cell).

Diethyl 1-Methyl-3-oxobutylmalonate Ethylene Ketal (4). A mixture of 57.9 g (0.237 mol) of diethyl 1-methyl-3-oxobutylmalonate (**3**),[39] 208 g of ethylene glycol, 2.3 g of *p*-toluenesulfonic acid, and 3500 ml of benzene was refluxed under a Dean-Stark tube for 43 hr. The cooled reaction mixture was washed with 5% potassium hydroxide solution, water, and brine solution and dried (Na_2SO_4). Distillation of the liquid remaining after removal of benzene gave 60.3 g (88%) of **4**: bp 115–117° (0.04 mm); $n^{22}D$ 1.4450; ir (CH_2Cl_2) 1735 cm^{-1} (C=O); the nmr ($CDCl_3$) showed two overlapping triplets and a doublet at δ 0.53–0.68 [CH_3CH_2 and $CH(CH_3)$], a singlet at 0.72 (CH_3CO_2), a doublet at 3.46 [$CH(CO_2Et)_2$], a singlet at 3.92 (OCH_2CH_2O), and a quartet at 4.18 ppm (CH_3CH_2).

Anal Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.57; H, 8.38.

3-Methyl-5-oxohexanoic Acid (5). To a refluxing solution of 100 g of potassium hydroxide in 100 ml of water was added dropwise 111.4 g (0.386 mol) of ketal diester (**4**). After the addition, the reaction mixture was refluxed an additional 4 hr. Water (100 ml) was added to the reaction and 100 ml of distillate collected (ethanol–water azeotrope). The reaction mixture was cooled in an ice bath and acidified to pH 1 with concentrated hydrochloric acid. The acid solution was refluxed overnight, cooled, and extracted with chloroform. The dried (Na_2SO_4) extracts were concentrated on a rotary evaporator. The resulting liquid was distilled under reduced pressure to give 36.6 g (73%) of **5**: bp 114° (0.5 mm); $n^{25}D$ 1.4442; ir (CH_2Cl_2) 1710 (C=O); the nmr ($CDCl_3$) showed a doublet at δ 1.04 (>$CHCH_3$), a singlet at 2.16 (CH_3CO), and a singlet at 10.0 ppm (acid OH).

Anal Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.40; H, 8.23.

Resolution of 3-Methyl-5-oxohexanoic Acid (5). To a solution of 100 g (0.83 mol) of *l*-(−)-α-methylbenzylamine in 4700 ml of ethyl ether was added 118.5 g (0.82 mol) of **5** in 200 ml of ethyl ether. The solid which separated after standing at 10° for 3 days was isolated by filtration, and the filtrate was retained for further examination. The salt obtained was recrystallized five more times from ethyl ether to give 21.1 g of *l*-(−)-α-methylbenzylamine (−)-3-methyl-5-oxohexanoate as a hygroscopic salt.[40]

Anal Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.03; H, 8.70; N, 5.35.

To a solution of the salt in 200 ml of water was added 10 ml of concentrated hydrochloric acid, and the solution was extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and concentrated on a rotatory evaporator. The resulting liquid was distilled to give 7.6 g of (−)-**5**: bp 110° (0.05 mm); $[\alpha]^{29.5}D$ −2.3°; $[\alpha]_{365}^{29.5}$ −33.2° (*c* 0.519, C_2H_5OH). The ir and nmr spectral properties were identical with those of (±)-**5**.

The filtrates retained from the preparation of (−)-**5** were concentrated *in vacuo* and the free acid regenerated. The liquid obtained was distilled to give 75.4 g (0.52 mol) of partially resolved **5**. A solution of the acid in 200 ml of ethyl ether was added to 63.3 g (0.52 mol) of *d*-(+)-α-methylbenzylamine in 2000 ml of ethyl ether. The solid which separated on standing at 10° for 3 days was recrystallized three more times from ethyl ether to give 18.5 g of *d*-(+)-α-methylbenzylamine (+)-3-methyl-5-oxohexanoate as a hygroscopic salt.[40]

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.11; H, 8.92; N, 5.45.

Using the same procedure described for the preparation of (−)-**5**, the salt above gave 8.2 g of (+)-**5**: bp 110° (0.05 mm); $[\alpha]^{26}D$ +2.8°; $[\alpha]_{365}^{26}$ +35° (*c* 0.50, C_2H_5OH).

In a separate experiment conducted in the same manner as above, (+)-**5** having $[\alpha]^{23}D$ +2.64°, $[\alpha]_{365}^{23}$ +33.6° (*c* 0.568, C_2H_5OH), was obtained.

Determination of the Optical Purity of (+)- and (−)-5. The salt (0.200 g) obtained from (±)- or (+)-**5** with *l*-(+)-2-methylbenzylamine was dissolved in 10 ml of tetrahydrofuran containing 0.202 g of 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), and the mixture was heated at 50° for 16 hr. The reaction mixture was concentrated on a rotary evaporator, and the remaining residue was dissolved in benzene. The benzene extracts were washed with 5% hydrochloric acid solution and water, and dried (Na_2SO_4). The benzene solution was concentrated to a small volume and chromatographed on alumina using benzene–chloroform (3:1) as the eluent. The product fractions were combined to give 0.150–0.175 g of the amides from (±)- and (+)-**5**. The 100-MHz nmr spectrum ($CDCl_3$) of 0.026 g of the mixture of diastereomers obtained from (±)-**5** in the presence of 0.120 g of Eu(fod)$_3$ exhibited two doublets at δ 4.82 and 5.08 and two singlets at 5.85 and 6.02 ppm for the NCHCH_3 and CH_3CO resonances, respectively. The 100-MHz nmr spectrum ($CDCl_3$) of the amide (**6b**) from (+)-**5** ($[\alpha]_{365}$ +35°) showed one doublet at 5.08 and one singlet at 6.02 ppm for the NCHCH_3 and CH_3CO resonances indicating that this compound is optically pure. The calculated optical purities of (−)-**5** ($[\alpha]_{365}$ −33.2°) and (+)-**5** ($[\alpha]_{365}$ +33.6°) are 95 and 96%, respectively. These values were substantiated by nmr analyses of their respective α-methylbenzylamine amides as described for the analysis of the racemic amide of (+)-**5**.

***cis*- and *trans*-3,5-Dimethylvalerolactones (7 and 8). (A) Sodium Borohydride Method.** To a cooled (ice bath) solution of 5.5 g (0.038 mol) of (−)-, (+)-, or (±)-**5** in 50 ml of 95% ethanol was added 1.45 g of sodium hydroxide in 8 ml of water. To this solution was added portionwise 2.93 g of sodium borohydride, and the reaction mixture was stirred an additional 2–4 hr after the addition. The reaction mixture was acidified with hydrochloric acid and 19 g of tartaric acid was added. The resulting clear solution was extracted with ether. The extracts were washed with water, dried (Na_2SO_4), and concentrated on a rotary evaporator to give a mixture of *cis*- and *trans*-3,5-dimethylvalerolactones, which was distilled under reduced pressure to give 4.2–4.3 g (86–88%) of a mixture of **7** and **8**; bp 65–67° (0.08 mm).

(B) Catalytic Reduction. A solution of 2.17 g (0.015 mol) of (−)-**5** in 40 ml of absolute ethanol containing 1 g of platinum oxide was shaken on a Parr hydrogenator under 50 lb of hydrogen pressure for 3 days. The catalyst was separated by filtration and the filtrate concentrated on a rotary evaporator. The remaining liquid was distilled under reduced pressure to give 1.66 g (76%) of a mixture of *cis*- and *trans*-3,5-dimethylvalerolactones; bp 50–55° (0.05 mm). Reduction of 10 g (0.069 mol) of (±)-**5** under similar conditions gave 6.5 g (72%) of racemic *cis*- and *trans*-3,5-dimethylvalerolactones; bp 75–77° (2 mm).

Separation of *cis*- and *trans*-3,5-Dimethylvalerolactones. Method A. A solution of 5.7 g (0.045 mol) of a mixture of *cis*- and *trans*-3,5-dimethylvalerolactones obtained from (−)-, (+)-, or (±)-**5** in 25 ml of benzene containing 25 ml of freshly distilled pyrollidine was refluxed under a Dean-Stark tube for 24 hr. The benzene and excess pyrollidine were removed on a rotary evaporator. An ir spectra of the remaining liquid showed the absence of lactone carbonyl. The mixture of hydroxyamides was chromatographed on 1800 g of Woelm neutral alumina (II) eluting first with benzene and then with the following solvents: benzene and chloroform mixture, chloroforms, and finally 3% methanol in chloroform. One amide (I) was eluted with benzene and chloroform eluents and

Table IV
Optical Rotations of *cis*- and *trans*-3,5-Dimethylvalerolactone Samples[a]

Compd (no.)	Optical rotations (deg), $[\alpha]_D$; $[\alpha]_{365}$, c (CH_3OH)
(3*RS*,5*SR*)-*cis* (**7**)	0
(3*RS*,5*RS*)-*trans* (**8**)	0
(3*S*,5*R*)-*cis* (**7a**)[b]	+6.15; +14.99, 0.521
(3*S*,5*S*)-*trans* (**8a**)[b]	−62.7; −224, 0.498
(3*R*,5*S*)-*cis* (**7b**)	−6.18; −15.0, 0.534
(3*R*,5*R*)-*trans* (**8b**)	+63.2; +222, 0.498

[a] The optically active lactones reported in this table were prepared from (+)- and (−)-**5** having $[\alpha]_{365}$ +33.6 and −33.2°, respectively. [b] The values for (3*S*,5*R*)-*cis* (**7a**) and (3*S*,5*S*)-*trans* (**8a**) previously reported (ref 6d) were −7.33 and −68.17°, respectively. The rotation of the (3*S*,5*R*)-*cis* (**7a**) previously reported (ref 6b) actually possessed a positive rotation.

the other amide (II) with 3% methanol in chloroform eluent. The progress of the chromatography and the purity of the amides were determined by tlc analysis on alumina plates using chloroform as the eluent. The plates were developed in an iodine chamber. The tubes containing pure amide I and amide II were combined and concentrated to give 2.11–2.24 and 2.39–2.68 g of amides I and II, respectively. The ir spectra (CH_2Cl_2) of both amides showed broad absorption at 3400 (OH) and 1675 cm^{-1} (amide carbonyl), and only slight differences were apparent in the fingerprint region of the spectra; the nmr ($CDCl_3$) of amides I and II were also very similar. Amide I showed doublets at δ 1.00 and 1.17 ppm for the 3- and 5-methyl groups whereas amide II showed doublets at δ 1.00 and 1.15 ppm for the same groups. The mass spectra of amides I and II were essentially identical: (70 eV) *m/e* (rel intensity) 199 (8, molecular ion), 181 (43), 166 (93), 140 (14), 124 (21), 113 (100), 98 (71), and 85 (36).

Amide I was refluxed in 10% sodium hydroxide solution for 4 hr. The cooled reaction mixture was acidified with concentrated hydrochloric acid and extracted with ether. Concentration of the dried (Na_2SO_4) ether extracts followed by evaporative distillation of the liquid obtained gave 82–85% of *cis*-3,5-dimethylvalerolactone (**7**): $n^{25}D$ 1.4445; ir (CCl_4) 1735 cm^{-1} (C=).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.59; H, 9.19.

Amide II was converted to *trans*-3,5-dimethylvalerolactone (**8**) in exactly the same manner as described for the conversion of amide I to **7**: $n^{25}D$ 1.4476; ir (CCl_4) 1736 cm^{-1} (C=O).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.54; H, 9.54.

Glc of all the isomers of **7** and **8** showed only one peak on both columns A and B. The ^1H nmr and ^{13}C nmr properties of **7** and **8** are listed in Tables I and III, respectively. The optical properties of **7** and **8** are listed in Table IV.

Method B. The lactones **7** and **8** could also be separated by preparative gas–liquid chromatography on a Model 700 Autoprep GC using a 15 ft × ⅜ in. copper column packed with 20% DEGS on 60–80 Chromosorb W AW-DMCS (165°, flow rate 150 ml/min of helium). For isolation 30-μl samples were processed on this column. The cis isomer (**7**) had a retention time of 48 min, and the trans isomer (**8**) had a retention time of 59 min 30 sec. The collection efficiency was 75–80%. The $n^{25}D$, ir, and ^1H nmr of the lactones **7** and **8** separated by this procedure were identical with those separated by method A.

(*R*)-(+)-Methyl 4-Methyl-6-oxoheptanoate Ethylene Ketal (10). To a solution of 19.6 g of (+)-4-methyl-6-oxoheptanoic acid[36] in 100 ml of ether was added an ethereal diazomethane solution until all reaction ceased. The solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Reduced pressure distillation of the crude product yielded 18.6 g (88%) of methyl 4-methyl-6-oxoheptanoate: bp 92° (3 mm); ir (CH_2Cl_2) 1712 (ketone C=O) and 1735 cm^{-1} (ester C=O).

A mixture of 18.1 g (0.105 mol) of methyl 4-methyl-6-oxoheptanoate, 65 g of ethylene glycol, and 0.7 g of *p*-toluenesulfonic acid was refluxed 4 hr under a Dean-Stark tube. The cooled solution was washed with 5% KOH (2 × 250 ml), water (1 × 250 ml), and saturated brine (1 × 250 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was fractionated at reduced pressure to yield 17.02 g (75%) of the title compound: bp 71° (0.06 mm); $n^{25}D$ 1.4414; d^{22} 1.033; $[\alpha]^{24}D$ +2.68° (neat).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.08; H, 9.32. Found: C, 60.90; H, 9.20.

(*R*)-(+)-7,7-Diphenyl-7-hydroxy-4-methyl-2-oxoheptane Ethylene Ketal (11). To a solution of 15.8 g (0.073 mol) of **10** in 75 ml of dry ethyl ether was added 58.5 ml (an excess) of a 3 *M* phenylmagnesium bromide solution in ethyl ether, and the mixture was refluxed for 5 hr. The cooled reaction mixture was poured onto ice, and glacial acetic acid was added until the solids dissolved. The ether phase was separated and combined with the ether extract (7 × 100 ml) of the aqueous phase, washed with 0.4% $NaHCO_3$ (5 × 100 ml) and saturated brine (1 × 100 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude solid obtained was purified by a combination of chromatography on Woelm aluminum oxide (III) (benzene eluent) and recrystallization from a cyclohexane and hexane mixture. A total of 17.64 g (71%) of **11** was obtained, mp 75–80°. The analytical sample prepared by recrystallization from a cyclohexane and hexane mixture had mp 80–81°; $[\alpha]^{22.5}D$ +5.19° (c 1.54, C_2H_5OH); ir (CH_2Cl_2) 3595 and 3380 (OH) and 1595 cm^{-1} (aromatic); nmr ($CDCl_3$) showed a doublet at δ 0.93 (>CHCH_3, J = 5.7 Hz), a singlet at 1.23 (CH_3CO_2), a singlet at 3.80 (OCH_2CH_2O), and a multiplet at 7.10–7.61 ppm (aromatic); mass spectrum (70 eV) *m/e* 340 for molecular ion.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.90; H, 8.30.

(*R*)-(+)-7,7-Diphenyl-4-methyl-6-hepten-2-one (12). A solution of 14.88 g (0.0437 mol) of **11** in 450 ml of chloroform containing 3 ml of water and 0.45 g of *p*-toluenesulfonic acid was refluxed for 1 hr. The cooled reaction mixture was washed with water, 0.4% sodium bicarbonate solution, and water. The organic layer was dried (Na_2SO_4) and concentrated on a rotary evaporator. The liquid obtained was distilled under reduced pressure to give 10.76 g (89%) of **12**: bp 178° (0.02 mm); $n^{25}D$ 1.5705; $[\alpha]^{23.5}D$ +15.54° (c 2.02, C_2H_5OH); ir (CH_2Cl_2) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) showed a singlet at δ 2.01 (CH_3CO), a triplet at 6.11 (CH=CH_2), and a multiplet centered at 7.23 ppm (aromatic protons).

Anal. Calcd for $C_{20}H_{22}O$: C, 86.28; H, 7.97. Found: C, 86.24; H, 7.98.

(*S*)-(+)-Methyl-5-oxohexanoic Acid (5) Prepared from 12. A solution of ruthenium tetroxide was prepared by adding 4.0 g of sodium metaperiodate in 40 ml of water to a suspension of 1.0 g of ruthenium dioxide in 300 ml of acetone (distilled from potassium permanganate) and 120 ml of water. To this solution was added dropwise a solution of 8.5 g (0.003 mol) of **12** in 400 ml of acetone over a 2-hr period. The solution turned dark as **12** was added, and the ruthenium tetroxide was regenerated by adding a solution of 60 g of sodium metaperiodate in 600 ml of acetone–water (1:1) as needed. After the addition, more of the solution was added as the mixture darkened in color. Two hours after the addition was completed, 400 ml of isopropyl alcohol was added. The reaction mixture was filtered through a Celite pad and the precipitate washed well with acetone. The filtrate was concentrated on a rotary evaporator until an oil began to separate. This mixture was extracted with chloroform (5 × 200 ml). The extracts were combined and extracted with 400 ml of 5% sodium hydroxide solution in three portions. These extracts were cooled in an ice bath, acidified with concentrated hydrochloric acid, and extracted with chloroform. The chloroform fraction was dried (Na_2SO_4) and concentrated on a rotary evaporator to give a yellow liquid. Distillation under reduced pressure gave 2.74 g (62%) of (+)-**5**:[41] bp 105° (0.08 mm); $n^{25}D$ 1.4451; $[\alpha]^{25}D$ +1.96° (c 0.46, C_2H_5OH); $[\alpha]^{23}D$ +4.52 (neat). The ir and nmr spectra of this sample of (+)-**5** were identical with the sample prepared by resolution of (±)-**5**.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.13; H, 8.23.

Registry No.—**3**, 52920-95-3; **4**, 52920-96-4; (±)-**5**, 52920-97-5; (−)-**5**, 52949-94-7; (−)-**5** (−)-α-methylbenzylamine salt, 52949-95-8; (+)-**5**, 52949-96-9; (+)-**5** (+)-α-methylbenzylamine salt, 52949-97-0; **6a**, 52920-98-6; **6b**, 52920-99-7; **7**, 52949-98-1; **7a**, 32747-16-3; **7b**, 52949-99-2; **8**, 52950-00-2; **8a**, 32747-17-4; **8b**, 52950-01-3; **9**, 52921-00-3; **9** methyl ester, 52921-01-4; **10**, 52921-02-5; **11**, 52921-03-6; **12**, 52921-04-7; amide I, 52921-05-8; amide II, 52921-06-9; (−)-α-methylbenzylamine, 2627-86-3; (+)-α-methylbenzylamine, 3886-69-9; pyrrolidine, 123-75-1.

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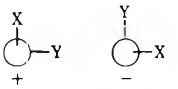

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(41) The acid (+)-**5** was also prepared by ozonolysis of **12** using a formic acid 30% hydrogen peroxide work-up. However, the yield of acid (+)-**5** obtained by this method was low (14%), and the sample was not as pure as the sample obtained by ruthenium tetroxide oxidation.

The pH Independent Equilibrium Constants and Rate Constants for Formation of the Bisulfite Addition Compound of Isobutyraldehyde in Water[1]

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The magnitudes of the apparent equilibrium constants for the formation of adduct in aqueous solutions of isobutyraldehyde and sodium bisulfite were determined spectrophotometrically and titrimetrically from pH 2.3 to 12.8 at 25°. The equilibrium constant for the addition of sulfite ion to isobutyraldehyde is 3.70 M^{-1} (at zero ionic strength) and the pK_a of the sodium bisulfite addition compound of isobutyraldehyde is 11.32 (at zero ionic strength). Rate constants were determined spectrophotometrically using potassium triiodide as a scavenger. General acids and general bases appear to have no effect on the rate of dissociation over the pH range of 4.4–7.8 and the rate-determining step is clearly a unimolecular decomposition of the doubly charged anion. The pH independent rate constants k_d and k_f, for decomposition and formation of this dianion, respectively, are 3800 sec^{-1} and 14,000 M^{-1} sec^{-1}, respectively.

Among the types of reactions used to characterize certain reactive ketones and aldehydes is the formation of sodium bisulfite addition compounds, which may at a later time be decomposed to yield the aldehyde or ketone. The fact that the carbonyl compound is recoverable is responsible for the role this reaction has as a means of separating aldehydes and reactive ketones from mixtures that contain other organic substrates. It is surprising that so little information is available with regard to the equilibria, kinetics, and mechanism of adduct formation and decomposition.

It is known that bisulfite addition compounds have at least largely the α-hydroxy sulfonate rather than the α-hydroxy sulfite structure.[2-5] Shriner and Land showed that the true structure in the case of acetaldehyde is of the former type by using an unambiguous method of synthesis.[6] Physical methods were used by Stelling and later by Caughlan and Tarter to determine the structure of the adduct in solution.[7,8] From the Raman spectra of saturated solutions (at 60°) it was concluded that there were no polymeric forms of the adduct, and that the sodium bisulfite adducts of formaldehyde, acetaldehyde, propionaldehyde, and acetone are all derivatives of α-hydroxy sulfonates. We know of no evidence that these adducts exist in solution in more than one form. However, the possibility that a small fraction of the adduct is present in the form of the α-hydroxy sulfite was not always considered in previous studies. We therefore investigated this possibility.

We are aware of only two other reports on the equilibration of an aldehyde or ketone and sulfite ion in alkaline solution,[9,10] and of no other studies where a significant portion of the curve relating the apparent equilibrium constant and pH has been determined for aliphatic aldehydes. For these reasons and in order to learn more about the possible relationships between rate constants and equilibrium constants for one-step Lewis acid–base reactions, we have studied the addition of sodium bisulfite to isobutyraldehyde over the pH range 2.3–12.8.

Experimental Section

Isobutyraldehyde (bp 63.5–64.0°) was freshly distilled before preparing solutions. Borax, boric acid, cacodylic acid (Fisher Scientific), sodium dihydrogen phosphate, sodium bicarbonate, and sodium barbitol were commercially available and used without further purification. Acetic acid was purified by several recrystallizations at 16.6°. Trifluoroethanol was shown to be pure by glpc analysis. The concentration of formic acid (Mallinckrodt 88% analytical reagent) was determined titrimetrically.

Stopped-flow experiments were conducted on a Durrum–Gibbson stopped-flow spectrometer equipped with a D-150 modular control unit. The photomultiplier signal was recorded as millivolt output on a Nicolet 1090 digital oscilloscope. Nmr spectral results were obtained on a Varian Model A-60A spectrometer using TMS as the reference. Ultraviolet and visible spectra were recorded on a Cary Model 1605 spectrometer. The pH measurements were made on a Radiometer Type 26 pH meter with a Type K401 reference electrode and Type G202C glass electrode. Sodium ion corrections to the pH were made where necessary.

Stopped-flow experiments were begun by placing a solution of isobutyraldehyde and sodium sulfite (approximately 0.001 *M* in each) in one of two storage reservoirs and a solution of potassium triiodide (approximately 0.003 *M*) in the other. Equal volumes of the two solutions, which were buffered and thermostated at 25°, were mixed by actuating the stopped-flow apparatus. The two solutions contained enough potassium iodide to give an ionic strength of 0.1 for the final mixture. The pH of the reaction mixture was determined after it exited from the apparatus. Slower reactions were followed using the Cary 1605. A solution of isobutyraldehyde and sodium sulfite was first prepared and to this solution was added an equal volume of potassium triiodide solution. A fraction of the solution was then placed in the thermostated cuvette, and the other portion was used for determining the pH.

Aqueous solutions of sulfite are easily oxidized, the extent of oxidation depending greatly on the method of preparation and handling. It was necessary to titrate the standard solution of sulfite ion before a series of experiments could be conducted even though we had taken elaborate precautions to prevent oxidation of sulfite. Blank experiments were conducted to show that there was no appreciable oxidation of sulfite solutions to which isobutyraldehyde had been added over the same period of time that was required to experimentally determine the apparent equilibrium constant in a solution to which isobutyraldehyde had been added. To obtain a standard solution of sulfite ion, solid sodium bisulfite was weighed, dissolved in double distilled degassed (boiled) water, and placed in a large reservoir under nitrogen. The reservoir was attached to a buret that could be filled or emptied without introducing oxygen from the atmosphere. This entire assembly was kept under a positive pressure of nitrogen. A measured volume of standard potassium iodate solution was used to generate a predetermined quantity of iodine in a 125-ml erlenmeyer flask to which had been added 0.5 *N* hydrochloric acid and potassium iodide. The volume of sulfite solution that was necessary to reach a starch–iodine end point and the number of milliequivalents of iodine originally present permitted the determination of the sulfite solution's normality. The difference between this and the value based on the weight of sodium bisulfite used was attributed to oxidation to sulfate.

The apparent equilibrium constant was determined titrimetrically as follows. A weighed amount of isobutyraldehyde was dissolved in doubly distilled water and diluted to 100 ml; 75 ml of this solution was placed in a 250-ml volumetric flask, which was then filled to the mark with standard sulfite solution, sealed with paraffin, and allowed to equilibrate thermally in a 25° water bath in a 25° laboratory. A known volume of this isobutyraldehyde–sulfite solution was added to the buffer solution in one of the seven or eight 25-ml volumetric flasks that were also in the 25° bath. This first solution was allowed to equilibrate and samples were removed for analysis and determining the pH before a second solution was prepared. An aliquot of the equilibrated mixture of sulfite and isobutyraldehyde was quenched by adding it with rapid stirring to a chilled solution of 0.5 *N* hydrochloric acid and iodine. The amount of excess iodine was determined by back-titrating to a starch–iodine end point with sodium thiosulfate.

The apparent equilibrium constants were also determined spectrometrically at 25°. A solution of isobutyraldehyde and sulfite ion was placed in one reservoir and a solution of the appropriate buffer or sodium hydroxide in the second reservoir of the stopped-flow apparatus, which was then actuated to mix equal volumes of the two solutions. A blank run was made following the same procedure except that distilled water was used in place of isobutyraldehyde solution. The concentration of free isobutyraldehyde at equilibrium was determined by subtracting the absorbance of the blank solution from the absorbance of the first solution and then dividing by the cuvette path length and the extinction coefficient. The apparent equilibrium constants were determined before aldol condensation reactions could interfere. The pH was determined in the same manner as in the kinetic experiments.

Sodium 1-Hydroxy-2-methylpropanesulfonate. In order to study the rate of dissociation of the complex and to study the approach to equilibrium from the other side, we prepared the sodium bisulfite addition compound of isobutyraldehyde in 95% ethanol. The product was recrystallized several times from ethanol, and dried in various ways. Samples were analyzed for free sodium bisulfite by adding them to 0.5 *M* hydrochloric acid and titrating iodometrically. They were analyzed for $Me_2CHCH(OH)SO_3Na$ by iodometric titration in a Borax buffer at pH 7, where the bisulfite addition compound decomposes rapidly, and correcting for the free bisulfite that had been found. These analyses showed that the material contained 86–91% bisulfite addition compound. Material dried in a current of air for 15–90 min contained only 0.1–0.2% free sodium bisulfite. Material that had been subjected to heat and high vacuum contained considerably more free sodium bisulfite, presumably as a result of loss of isobutyraldehyde from the addition compound. The pmr spectrum in 100.0% D_2O to which CD_3CO_2D had been added, τ 5.31 (s, 2.73, *H* OD), 5.81 (d, 0.95, J = 5 Hz, $CHSO_3$), 8.97 (d, 3.06, J = 6.5 H Hz, CH_3), 9.01 (d, 3.06, J = 6.5 Hz, CH_3), and 7.90 ppm (m, 1.05, Me_2CH), of a sample dried at 0.05 mm at room temperature for 24 hr showed no ethanol peaks nor evidence for any substances other than the bisulfite addition compound and water, of which there is seen to be about 0.86 mol of water/mol of addition compound in this sample. Sousa and Margerum described good evidence that the crystalline sodium bisulfite addition compound of benzaldehyde is a hemihydrate.[11] Elemental analysis of a sample dried at 0.05 mm at room temperature for 24 hr gave fairly good agreement with a hemihydrate structure. Therefore samples of this material were assumed to contain only the amounts of sodium bisulfite addition compound and free sodium bisulfite determined by analysis and water.

Anal. Calcd for $C_8H_{20}Na_2O_9S_2$: C, 25.95; H, 5.44; S, 17.32. Found: C, 26.02; H, 5.50; S, 17.97.

Results

The apparent equlibrium constant is defined by eq 1, in which adduct refers to all states of protonation of the bisul-

$$K_{app} = [\text{adduct}]/([i\text{-PrCHO}][\text{free sulfite}]) \quad (1)$$

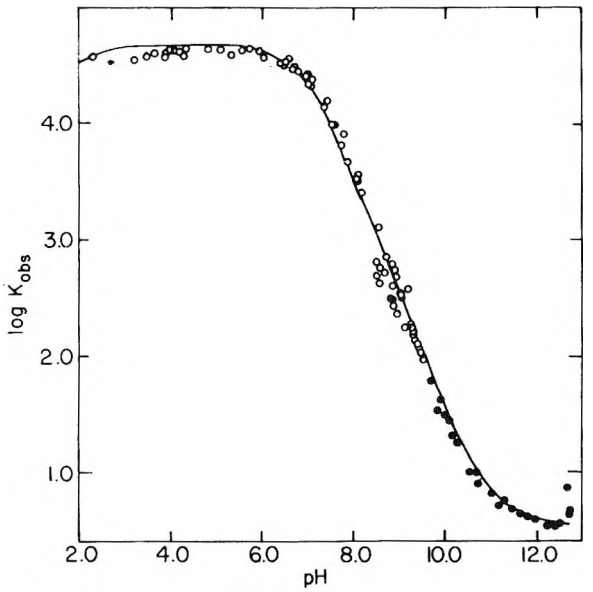


Figure 1. Log K_{app} *vs.* pH for isobutyraldehyde and sodium bisulfite in water at 25° (○, titrimetric; ●, spectrometric).

fite addition compound and free sulfite refers to sulfite and bisulfite ions and sulfur dioxide (essentially the only form in which "sulfurous acid" exists at equilibrium). In the titrimetric experiments the adduct concentration was set equal to the total concentration of sulfite known to be in the solution minus the concentration of free sulfite. The concentration of uncomplexed unhydrated aldehyde was then set equal to the total concentration of aldehyde in the solution minus the concentration of adduct and the concentration of aldehyde hydrate and its conjugate base calculated from the equilibrium constants for hydration of the aldehyde and for the acidity of the hydrate.[12] For example, an equilibrated solution 0.01412 *M* in total aldehyde and 0.006892 *M* in total sulfite at pH 9.258 and ionic strength 0.138 was found to be 0.003112 *M* in free sulfite. These data give a value of 188 M^{-1} for K_{app}. In the spectrophotometric experiments the adduct concentration was calculated from the difference between the total concentration of aldehyde and that seen spectrally to be present at equilibrium (allowing for hydration and hydrate acidity). The 92 values of K_{app} obtained over the pH range 2.3–12.8 are plotted logarithmically against pH in Figure 1 and are listed in Table III (in the miniprinted section of this paper).

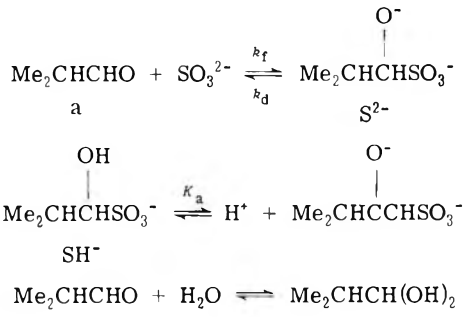
Preliminary spectrophotometric kinetic studies carried out around pH 11 showed that the decomposition of adduct produced an increase in absorbance at the 285-nm aldehyde maximum followed by a decrease as the aldehyde was hydrated. It therefore seemed simpler to follow the reaction by a method similar to that of Stewart and Donnally[10] in which triiodide ions react with the sulfite ions as rapidly as they are formed and thus prevent reversal of the decomposition of the adduct. First-order rate constants were calculated from eq 2 in which $[I_3^-]_0$ is the initial and $[I_3^-]_\infty$ the final triiodide concentration (measured spectrophotometrically) and $[I_3^-]$ is the concentration at time *t*.

$$k_{obsd}t = \ln [([I_3^-]_0 - [I_3^-]_\infty)/([I_3^-] - [I_3^-]_\infty)] \quad (2)$$

Discussion

The reaction mechanism shown in Scheme I was assumed to be operating. Equilibrium constants for the formation of S^{2-} and SH^- and for the acidity of SH^- are defined in eq 3–5. At zero ionic strength these equilibrium constants are related to each other by eq 6, in which $K_{HSO_3^-}$ is the acidity constant for bisulfite ions. The ap-

Scheme I



$$K_{S^{2-}} = [S^{2-}]/([a][SO_3^{2-}]) \quad (3)$$

$$K_{SH^-} = [SH^-]/([a][HSO_3^-]) \quad (4)$$

$$K_a = [H^+][S^{2-}]\gamma_\pm^4/[SH^-] \quad (5)$$

$$pK_a = pK_{HSO_3^-} + \log K_{SH^-} - \log K_{S^{2-}} \quad (6)$$

parent equilibrium constant may be expressed as shown in eq 7, in which $\gamma_\pm$ is the activity coefficient of a single-charged ion and K_{SO_2} is the acidity constant ($[H^+][HSO_3^-]/[SO_2]$) for sulfurous acid. Scheme I does not allow for the

$$K_{app} = \frac{K_{S^{2-}} + K_{SH^-}[H^+]\gamma_\pm^4/K_{HSO_3^-}}{1 + ([H^+]\gamma_\pm^4/K_{HSO_3^-})(1 + [H^+]\gamma_\pm^2/K_{SO_2})} \quad (7)$$

formation of any electrically neutral α-hydroxysulfonic acid. Stewart and Donnally reported a pK_a value of −3 for the sulfonic acid derived from bisulfite and benzaldehyde. If the one derived from isobutyraldehyde is at all similar its concentration will be negligible at pH 2.3, the most acidic solution in which we made measurements.

Figure 1 shows that K_{app} approaches $K_{S^{2-}}$ at high pH. On dropping to intermediate pH's, it increases and becomes essentially equal to K_{SH^-} around pH 4.5 before starting to drop below pH 3 (because of the transformation of significant fractions of the sulfite to "sulfurous acid," pK 1.764[13]). A least-squares treatment[14] of the observed values of K_{app} carried out using a $pK_{HSO_3^-}$ value of 7.205 at zero ionic strength[13] and the Davies equation[15] to calculate $\gamma_\pm$ gave the values of $K_{S^{2-}}$, K_{SH^-}, and K_a listed in Table I. The line in Figure 1 was calculated from these values for an ionic strength of 0.10 (although the experimental ionic strength ranged from 0.023 to 0.286).

In the α-hydroxy sulfite alternative **1** to the usually accepted α-hydroxy sulfonate structure **2** for the anion of bi-

1 **2**

sulfite addition compounds, the sulfur is tetravalent. In view of the oxidizability of many tetravalent sulfur compounds, the ease of hydrolysis of sulfite esters,[16] and the fact that alkyl hydrogen sulfites (like sulfurous acid) are unknown, **1** would be expected to yield free sulfite or to behave like free sulfite when our equilibration solutions were quenched with acid before iodometric titration. Hence, when isobutyraldehyde is present in greater and greater excess over sulfite, the fraction of sulfite that is titratable should approach [1]/([1] + [2]). The results shown in Table II show that **1** comprises less than 0.3% of the total bisulfite addition compound. The bulky nature of the isopropyl groups should destabilize **2** relative to **1**, in which there is less branching at sulfur and the sulfur atom is farther from the isopropyl group. Hence if an α-hydroxy sulfite structure is ever important, it will probably have to be with a

Table I
Summary of pH Independent Equilibrium Constants and Rate Constants for Aldehyde–Bisulfite Equilibrations in Water

Structure	$K_{S^{2-}}$, M^{-1}	$10^{-5}K_{SH^-}$, M^{-1}	pK_a[a]	k_d, sec^{-1}	$10^{-5}k_f$, M^{-1} sec^{-1}	Ref
Isobutyraldehyde[b]	3.70	0.48	11.3	3800	0.14	This work
Formaldehyde[b]	220,000	~10^5	11.7	43	~95	9
Benzaldehyde[c]	65	0.10	9.6	180	0.12	10

[a] At zero ionic strength. [b] Temperature 25°. [c] Temperature 21°.

Table II
Per Cent Titrable Sulfite in the Presence of Excess Isobutyraldehyde at 25° in Water

Total aldehyde	$[NaHSO_3]_{total}$	$10^5[Sulfite]_{titrated}$	% titrable sulfite	pH	Buffer
0.08756	0.01222	0.0	0.00	5.669	Phosphate
0.07505	0.01222	2.2	0.18	5.662	Phosphate
0.05003	0.01222	2.2	0.18	5.666	Phosphate
0.03752	0.01222	3.1	0.25	5.663	Phosphate
0.02502	0.01222	6.2	0.52	5.670	Phosphate
0.01318	0.01217	147	12.10	6.097	Acetate
0.3592	0.01753	5.2	0.30	3.452	None
0.3353	0.01753	3.1	0.18	3.417	None
0.2395	0.01753	3.1	0.18	3.575	None
0.1916	0.01753	4.1	0.24	3.650	None
0.1197	0.10753	2.7	0.15	3.687	None
0.07184	0.01753	5.2	0.30	3.778	None
0.03592	0.01753	69.7	3.98	3.468	None
0.01895	0.01749	202	11.52	3.967	Acetate

much more crowded carbonyl compound than isobutyraldehyde.

The spectrophotometric method for determining K_{app} is most reliable for fairly small values of K_{app} but the values obtained above pH 11 are so small as to reduce the reliability somewhat. The proportion of isobutyraldehyde that forms a product can be regulated to some extent by adjusting the concentration of sulfite. If the concentration of sulfite ion greatly exceeds the concentration of isobutyraldehyde, a greater percentage of the aldehyde can be forced to react. Since we wanted to keep the ionic strength below 0.14 when possible, the amount of sulfite ion that could be used to force more of the aldehyde to react was limited. The fact that the apparent equilibrium constant becomes quite large as the solution is made more acidic also placed a limitation on the accuracy with which we could determine the concentration of isobutyraldehyde spectrophotometrically. It is for this reason that we chose to study the equilibrium below pH 9.5 by quenching an equilibrated mixture and then titrating to determine how much of the sulfite had not formed an adduct.

The titrimetric method for obtaining the equilibrium constant appears to be far more sensitive than the spectrometric method of analysis, particularly where a very large fraction of the isobutyraldehyde has reacted to form adduct. Unlike the spectrophotometric method of analysis, where the concentrations at equilibrium are directly obtained, the titrimetric method of analysis gives the concentration of sulfite ion in the much more acidic quenched solution. There are two criteria that must be met to assure that the calculated equilibrium constants are the correct constants. The first is that there be no change in the concentration of complexed sulfite ion as the reaction is quenched, and the second is that the rate of dissociation of the complex be negligible at the pH at which the solution is titrated. To learn whether the rate of dissociation is negligible at the pH at which the solutions were titrated, an equilibrated solution of isobutyraldehyde and sulfite ion was quenched in the manner described and the amount of excess iodine determined by back-titrating with sodium thiosulfate. However, in this experiment the amount of sodium thiosulfate necessary to remove the last trace of purple starch–iodine indicator was not added immediately. Instead, the solution was allowed to stand several minutes during which time the very faint purple color of the indicator persisted. The last drop of sodium thiosulfate was added after 30 min and the last trace of purple color was destroyed. If there had been a reaction during the 30-min experiment before adding thiosulfate, the color of the indicator would have faded. We estimate the rate constant for dissociation of the adduct to be less than 5.7×10^{-7} sec^{-1} under the conditions of the titration. The resulting error in the titration is negligible.

To learn whether the concentration of adduct shifts as equilibrated mixture of sulfite and isobutyraldehyde is quenched, let us compare the values of K_{app} determined titrimetrically with those determined spectrophotometrically. There is a portion of the curve in Figure 1 where points for the two types of K_{app} overlap (and agree satisfactorily). The pH range over which the two methods were compared could not be extended to more acidic solution because the spectrophotometric method became unreliable. Above pH 10 the equilibrium constant determined titrimetrically became larger than the value determined spectrophotometrically by amounts that increased with increasing pH. Apparently it was no longer possible to quench the reaction. The fact that the titrimetric equilibrium constants were too large suggests that significant amounts of free sulfite ion added to aldehyde during the addition of equilibrated solution to the hydrochloric acid and triiodide ion. The increase in acidity that occurs upon quenching is accompanied by an increase in K_{app}, which favors formation of more adduct. The dilution of the equilibrated mixture favors dissociation of adduct. The experimental results suggest that the presence of enough base in the equilibration solution will so slow the change in pH that the pH and the equilibration rate will remain high for a long enough time to permit an appreciable shift in equilibrium during quenching. We were unable to circumvent this difficulty even by using quenching solutions as acidic as 5 *N* hydrochloric acid. Since the rate of equilibrations is much slower in acidic solution, and since the spectrophotometric meth-

od and the titrimetric method are in good agreement where the initial solution's pH is less than or equal to 9.6, there is reason to believe that the K_{app} values determined titrimetrically at a pH less than 9.6 are reliable.

According to the mechanism in Scheme I, k_{obsd} should vary with the acidity as shown in eq 8. However, since the

$$k_{obsd} = k_d/(1 + [H^+]\gamma_\pm^4/K_a) \quad (8)$$

pK_a is 11.32 and the kinetics were not followed at any pH above 7.6, k_{obsd} may be expressed simply as $k_dK_a/([H^+]\gamma_\pm^4)$. Although some of the deviations from the straight line shown are larger than the variations in log $\gamma_\pm^4$ the plot is linear within the experimental uncertainty. This supports the adequacy of Scheme I. Nevertheless, the possibility of general catalysis by the constituents of the acetate and cacodylate buffers was examined by a least-squares treatment of the k_{obsd} values. All the catalysis constants for general catalysis were within the estimated standard deviations of zero. The least-squares[14] best values of k_d and k_f are listed in Table I. Also listed are values calculated from literature data on formaldehyde[9] and benzaldehyde.[10] Some of the additional literature data on bisulfite addition to carbonyl compounds are difficult to compare with those in Table I. Sousa and Margerum[11] described evidence that Gubareva[17] was not justified in assuming that dissociation of bisulfite addition compounds during iodometric titration of unacidified solutions may be neglected. Sousa and Margerum's experimental method should give their reaction solutions a pH around 5. A K value at 21° interpolated from their data at 13 and 23° is about 60% as large as the value reported by Stewart and Donnally at pH 5 (in a pH region where K changes only slowly with changing pH).[10] Uncertainty in the pH makes it impossible to obtain values of k_d and k_f from Sousa and Margerum's rate data, however. Blackadder and Hinshelwood studied the rates of dissociation of the bisulfite addition compounds of acetone, propionaldehyde, acetaldehyde, formaldehyde, chloral, and a number of benzaldehyde derivatives.[18] They determined rate constants at two pH's but gave no equilibrium data. Geneste, Lamaty, and Roque[19,20] studied the rates of dissociation of the bisulfite addition compounds of several aliphatic aldehydes and ketones and several benzal-

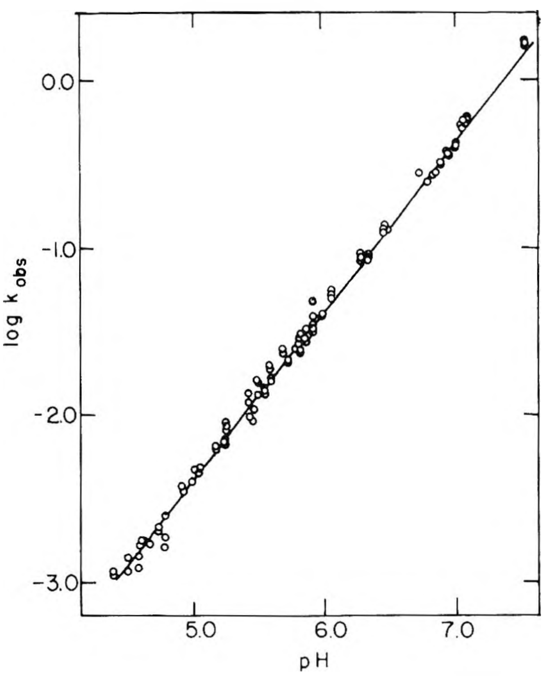


Figure 2. Log k_{obsd} *vs.* pH for sodium isobutyraldehyde bisulfite in water at 25° and 0.1 ionic strength.

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Table III. Sodium Isobutyraldehyde Bisulfite Equilibrations in Water at 25°.

pH	Total [aldehyde] M	Total [sulfite] M	Uncomplexed [sulfite] M	μ	Log K_{app}	Buffer
[illegible]	[illegible]	[illegible]	[illegible]	0.127	[illegible]	Formic Acid
[illegible]	[illegible]	0.00711[illegible]	[illegible]	0.115	[illegible]	''
[illegible]	[illegible]	[illegible]	[illegible]	0.115	[illegible]	''
[illegible]	0.004741	0.004741	0.0004189	0.118	[illegible]	''
[illegible]	0.003951	0.003951	[illegible]	0.118	4.551	''
3.920	0.007531	0.007531	[illegible]	0.118	[illegible]	Acetic Acid
[illegible]	0.004779	[illegible]	[illegible]	0.118	[illegible]	''
[illegible]	[illegible]	[illegible]	[illegible]	0.121	[illegible]	''
4.1[illegible]	0.005272	0.005272	0.0004257	0.116	[illegible]	''
4.2[illegible]	0.01634	0.01634	[illegible]	0.023	[illegible]	Cacodylic Acid
4.32[illegible]	0.004535	[illegible]	[illegible]	0.118	4.552	Acetic Acid
4.512	0.01172	0.01172	0.0007622	0.037	[illegible]	Cacodylic Acid
5.0[illegible]	0.01520	0.01520	0.001726	0.050	4.342	''
[illegible]	0.01366	0.01366	0.0007033	0.0[illegible]2	4.5[illegible]4	''
5.[illegible]	0.01217	0.01217	0.0006514	0.07[illegible]	[illegible]	''
[illegible]	0.01034	0.01034	0.0005972	0.089	[illegible]	''
[illegible]	0.009122	0.009122	0.000573[illegible]	0.102	4.[illegible]19	''
[illegible]	0.007[illegible]01	0.007[illegible]01	0.000540[illegible]	0.114	[illegible]	''
[illegible]	0.005[illegible]17	[illegible]	[illegible]	0.117	[illegible]	''
[illegible]	0.004305	0.004305	0.0005319	0.087	4.514	''
[illegible]	[illegible]093	[illegible]093	[illegible]	0.089	[illegible]	''
[illegible]	0.004081	[illegible]	[illegible]	0.125	[illegible]	''
[illegible]	0.003219	0.00321[illegible]	[illegible]	0.117	[illegible]	''
[illegible]	[illegible]	[illegible]	[illegible]	0.091	[illegible]	''
[illegible]	0.01941	0.01941	0.001013	0.034	4.455	Boric Acid
[illegible]	0.005255	[illegible]	0.0005425	0.093	4.409	Cacodylic Acid
[illegible]	0.005321	0.005321	0.0005382	0.134	4.422	''
7.010	0.002813	0.002813	0.0004168	0.117	4.344	''
7.041	0.01857	0.01857	0.001148	0.040	4.325	Boric Acid
7.125	0.005042	0.005042	0.0005435	0.094	4.38[illegible]	Cacodylic Acid
7.335	0.01772	0.01772	0.001359	0.047	4.151	Boric Acid

2

Table III. Continued

pH	Total [aldehyde] M	Total [sulfite] M	Uncomplexed [sulfite] M	μ	Log K_{app}	Buffer
7.44[illegible]	0.004832	0.004832	[illegible]	0.095	4.203	Cacodylic Acid
7.529	0.01688	0.01688	0.001579	0.053	3.992	Boric Acid
7.5[illegible]	0.004940	0.004940	0.0008235	0.138	3.987	Cacodylic Acid
7.721	0.01604	0.01604	0.001838	0.060	3.828	Boric Acid
7.7[illegible]	0.004727	0.004727	0.0008742	0.095	3.907	Cacodylic Acid
7.885	0.01519	0.01519	0.002080	[illegible]	3.686	Boric Acid
8.050	0.002511	0.002511	[illegible]	0.117	3.51[illegible]	Cacodylic Acid
8.072	0.01435	0.01435	0.002392	0.073	3.524	Boric Acid
8.110	0.004422	0.004422	0.00122[illegible]	0.096	3.558	Cacodylic Acid
8.211	0.01350	0.01350	0.0024[illegible]	0.060	3.395	Boric Acid
8.497	[illegible]	0.01160	[illegible]	0.037	2.814	Sodium Barbitol
8.505	0.01311	0.01435	[illegible]	0.131	[illegible]	Borax
8.547	0.01131	0.1181	0.003261	0.093	3.103	Boric Acid
8.571	[illegible]	0.01138	0.005577	0.037	2.762	Sodium Barbitol
8.564	0.01358	0.01519	[illegible]	0.131	2.634	Borax
8.645	0.008515	0.01116	0.005623	0.038	2.724	Sodium Barbitol
8.729	0.01505	0.01350	0.003911	0.053	2.856	''
8.772	0.01542	0.01688	0.007588	0.103	2.505	Borax
8.851	0.01099	0.01099	0.004909	0.023	2.606	Trifluoroethanol
8.859	0.01373	0.01232	0.004005	0.054	2.788	Sodium Barbitol
8.874	0.01620	0.01772	0.008317	0.132	2.425	Borax
8.912	0.01344	0.01205	0.004117	0.054	2.748	Sodium Barbitol
8.931	0.0131[illegible]	0.01180	0.004199	0.054	2.683	''
8.985	0.01[illegible]97	0.01657	0.008997	0.133	2.362	Borax
9.040	0.01238	0.01111	0.0048[illegible]2	0.054	2.525	Sodium Barbitol
9.040	0.01214	0.01089	0.004845	0.054	2.515	''
9.118	0.01774	0.01914	0.01003	0.133	2.253	Borax
9.182	0.008440	0.008440	0.004199	0.097	2.585	Boric Acid
9.255	0.01412	0.006892	0.003112	0.138	2.274	Borax
9.274	0.01412	0.008042	0.003791	0.138	2.260	''
9.300	0.01412	0.009190	0.004685	0.138	2.204	''

3

Table III. Continued

pH	Total [aldehyde] M	Total [sulfite] M	Uncomplexed [sulfite] M	μ	Log K_{app}	Buffer
9.305	0.01412	0.01034	0.005530	0.137	2.175	Borax
9.330	0.01412	0.01149	0.006470	0.137	2.135	''
9.366	0.01412	0.01379	0.008180	0.137	2.110	''
9.388	0.01412	0.01608	0.009795	0.137	2.117	''
9.431	0.01412	0.02068	0.01367	0.136	2.062	''
9.456	0.01412	0.02298	0.01570	0.136	2.035	''
9.528	0.01928	0.02110	0.01284	0.136	1.970	''
9.690	0.01099	0.01099	0.008349	0.032	1.785	Trifluoroethanol
9.910	0.01340	0.01535	0.01209	0.125	1.[illegible]29	Sodium Bicarbonate
9.817	0.01340	0.01535	0.01251	0.125	1.537	''
10.011	0.01340	0.01535	0.01266	0.126	1.502	''
10.094	0.01340	0.01535	0.01289	0.126	1.44[illegible]	''
10.167	0.01340	0.01535	0.01334	0.12[illegible]	1.32[illegible]	''
10.248	0.01340	0.01535	0.01359	0.126	1.250	''
10.535	0.01340	0.01535	0.01407	0.126	1.080	''
10.696	0.01340	0.01535	0.01407	0.125	1.080	''
10.73	0.02441	0.02441	0.02199	0.068	0.9035	Bisulfite-Sulfite ic
11.04	0.01099	0.01099	0.01053	0.041	0.8220	Trifluoroethanol
11.20	0.01099	0.01099	0.010[illegible]	0.042	0.7074	''
11.34	0.01099	0.01099	0.01059	0.044	0.7572	''
11.48	0.01099	0.01099	0.010[illegible]	0.04[illegible]	0.[illegible]62	''
11.66	0.01099	0.01099	0.01068	0.052	0.[illegible]397	''
11.80	0.02441	0.02441	0.02303	0.0[illegible]7	0.[illegible]208	Sodium Hydroxide
11.95	0.02441	0.02441	0.02307	0.0[illegible]7	0.[illegible]068	''
12.25	0.02441	0.02441	0.02331	0.087	0.5145	''
12.40	0.02356	0.02356	0.02250	0.138	0.5[illegible]	''
12.50	0.02356	0.02356	0.02246	0.12[illegible]	0.5540	''
12.67	0.02356	0.02356	0.02155	0.28[illegible]	0.8632	''
12.69	0.02356	0.02356	0.02232	0.196	0.[illegible]229	''
12.75	0.02356	0.02356	0.02221	0.23[illegible]	0.[illegible]702	''

4

Table IV. Tri-iodide and Sodium Isobutyraldehyde Bisulfite Kinetics in Water at 25° and 0.1 Ionic Strength.

k_{obs} x 10^3 sec^{-1}	$[AcH]_T$ M	$[CacH]_T$ M	pH	$[I_3^-]_T$ M	$[Substrate]_T$ M
1.12, 1.17	0.223[illegible]		4.389	0.003137	0.00084
1.41	0.1932		4.490	0.003137	0.000766
1.1[illegible]	0.1101		4.490	0.004182	0.000766
1.4[illegible], 1.23	0.1952		4.575	0.002091	0.000766
1.7[illegible]	0.09700		4.591	0.004182	0.000766
1.[illegible]	0.1[illegible]95		4.618	0.003137	0.000766
1.[illegible]	[illegible]		4.621	0.004182	0.000766
1.7[illegible], 1.7[illegible]	0.174[illegible]		4.[illegible]1	0.002091	0.000766
1.[illegible], 1.[illegible]1	0.1422		4.770	0.003137	0.000766
2.51	0.08077		4.785	0.004182	0.000766
3.[illegible]	0.0704[illegible]		4.918	0.004182	0.000766
3.51	0.12[illegible]		4.921	0.003137	0.000766
4.80, 4.50	0.06[illegible]		5.058	0.002928	0.000766
[illegible], [illegible].11	0.10[illegible]		5.200	0.003137	0.000766
7.17, [illegible].95	0.11[illegible]		5.245	0.002091	0.000766
[illegible], 7.1[illegible]	0.07[illegible]		5.253	0.002928	0.000766
[illegible], 8.44	[illegible]		5.2[illegible]4	0.003137	0.00085

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Table IV. Continued

k_{obs} x 10^3 sec^{-1}	$[AcH]_T$ M	$[CacH]_T$ M	pH	$[I_3^-]_T$ M	$[Substrate]_T$ M
13.[illegible], 12.[illegible]	0.09439		5.431	0.003137	0.00085
[illegible], 10.[illegible]	[illegible]24		5.470	0.004182	0.0007[illegible]
15.5, 1[illegible]	0.0927[illegible]		5.501	0.003137	0.00085
13.0, 13.7	0.09939		5.545	0.002091	0.00043
14.[illegible], 14.7	0.07124		5.549	0.002928	0.0007[illegible]
1[illegible], 1[illegible].4	0.0[illegible]84		[illegible]	0.003137	0.00085
1[illegible], 1[illegible].1	[illegible]77[illegible]		[illegible]	0.002091	0.00085
2[illegible], [illegible].7	[illegible]40		[illegible]	0.003137	0.00085
21.4, 2[illegible]	[illegible]		5.7[illegible]	0.002091	0.00043
27.4, 2[illegible]	[illegible]440		[illegible]	0.002091	0.00043
[illegible], 31.[illegible]	[illegible]		[illegible]	0.003137	0.00085
32.4, 4[illegible]	[illegible]42		[illegible]	0.002091	0.00043
2.13		[illegible]	4.727	0.004182	0.0014
5.97		[illegible]	[illegible].178	0.004182	0.00045
9.77		0.2[illegible]4	[illegible].440	0.004182	0.00045
24.4, [illegible], [illegible]		0.1[illegible]	[illegible].[illegible]32	0.004182	0.0014

6

Table IV. Continued

k_{obs} x 10^3 sec^{-1}	$[AcH]_T$ M	$[CacH]_T$ M	pH	$[I_3^-]_T$ M	$[Substrate]_T$ M
28.4, 27.7, 27.7		0.1251	5.860	0.004182	0.0019
34.2, 31.8, 32.1		0.1190	5.921	0.004182	0.0019
39.4, 38.9, 39.7		0.1098	6.020	0.004182	0.0014
51.3, 49.2, 52.5		0.09970	[illegible].0[illegible]7	0.004182	0.0014
85.9, 90.2, 85.0		0.07960	[illegible].305	0.004182	0.0014
86.8, 83.0, 83.9		0.13[illegible]	[illegible].329	0.0039	0.001
125, 131, 121		0.0[illegible]955	[illegible].471	0.004182	0.0014
124, 123, 122		0.1203	[illegible].491	0.0039	0.001
223, 223, 225		0.1051	[illegible].74[illegible]	0.0039	0.001
24[illegible], 249, 254		0.1003	[illegible].815	0.0039	0.001
274, 272, 276		0.09[illegible]4	[illegible].855	0.0039	0.001
304, 300, 297		0.0[illegible]	[illegible].872	0.004[illegible]	0.001
313, 31[illegible]		0.09[illegible]79	[illegible].899	0.0039	0.001
355, 362, 385		0.08773	[illegible].9[illegible]2	0.0039	0.001
400, 399, 412		0.09314	7.021	0.0039	0.001
498, 572, 540		0.0[illegible]94	7.075	0.004[illegible]	0.0014
580, 587, 592		0.05270	7.111	0.0039	0.001
1710, 1520, 1[illegible]		0.08449	7.[illegible]	0.0039	0.001

dehyde derivatives at pH 4. In none of these studies were enough data obtained to permit the calculation of k_d or k_f values.

Sørensen and Andersen report a pK_a of 11.7 for the bisulfite adduct of formaldehyde at 25°. We have calculated their data, allowing for the acidity of formaldehyde hydrate,[21] which had been neglected, and get a pK_a of 11.8 ± 0.5, $K_{S^{2-}}$ of (2.8 ± 2) × 10^5 M^{-1}, and K_{SH^-} of 10^{10} M^{-1}. The uncertainty in the pK_a and in both constants, $K_{S^{2-}}$ and K_{SH^-}, is attributable to the uncertainty in the intercept (which is related to the pK_a and very near to zero) in the plot correlating $1/K_{obsd}$ with $1/[OH^-]$. However, the magnitude of K_{SH^-} agrees well with the value of 1.6 × 10^{10} M^{-1} that can be obtained by combining the results of Skrabal and Skrabal[22] with the equilibrium constant for hydration of formaldehyde. Stewart and Donnally report a pK_a of 9.16 for the bisulfite adduct of benzaldehyde at 21° and ionic strength 0.10. This corresponds to a value of about 9.6 at zero ionic strength. Thus the thermodynamic pK_a values of compounds of the type $RCH(OH)SO_3^-$ are about 11.8, 11.3, and 9.6 when R is hydrogen, isopropyl, and phenyl, respectively. Acids of the type $RCH_2NH_3^+$ in which R is separated from the acidic proton by the same number of atoms, have pK_a values of 10.7, 10.4, and 9.3, at 26°, when R is hydrogen, isopropyl, and phenyl, resepctively.[23] Thus the effect of changing R from hydrogen to isopropyl in one series is the same, within the experimental uncertainty, as in the other. Phenyl, however, is an anomalously effective acid strengthening substituent in the α-hydroxy sulfonate series, not only by comparison to the ammonium ions but also by comparison to simple alcohols. Benzyl alcohol is about eight times as strong an acid as isobutyl alcohol and is only slightly stronger than methanol in isopropyl alcohol solution.[24] It may be relevant that if the titrimetric K_{app} values obtained above pH 10 by Stewart and Donnally were too large because of imperfect quenching, as ours were, too small a pK_a value for the bisulfite addition compound would result. We feel that their quenching method, in which acid but no cooling was employed, is probably not as effective as ours. However, if k_d is as much smaller for the benzaldehyde adduct as they report, perhaps a less effective quenching method would still be effective enough.

Acknowledgment. We thank the National Science Foundation for a grant that aided in the purchase of the nmr equipment used.

Registry No.—Sodium 1-hydroxy-2-methylpropanesulfonate, 13023-74-0; sodium bisulfite, 7631-90-5; isobutyraldehyde, 78-84-2.

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An Automated Preparative Liquid Chromatography System

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The design, construction, and operation of an automated preparative liquid chromatography system capable of separating multigram quantities of materials is presented. The system repetitively injects the sample, monitors the effluent, detects and separately collects, as programmed, entire chromatographic bands, then distills and reuses the eluting solvent.

The general utility of liquid chromatography systems is now widely appreciated, several commercial units being available. Because these commercial systems are basically analytical units which operate at high pressures and employ small columns packed with expensive adsorbents, they are not particularly well suited for the routine separation of multigram quantities of materials. Recognizing a need among organic chemists for instrumentation capable of such separations, we herein describe an automated low-pressure preparative liquid chromatography system which repetitively injects the sample, monitors the effluent, detects and separately collects, as programmed, entire chromatographic bands, then distills and reuses the solvent. Apart from its ability to separate multigram quantities through unattended repetitive operation, the system obviates the use of large quantities of solvent, substantially

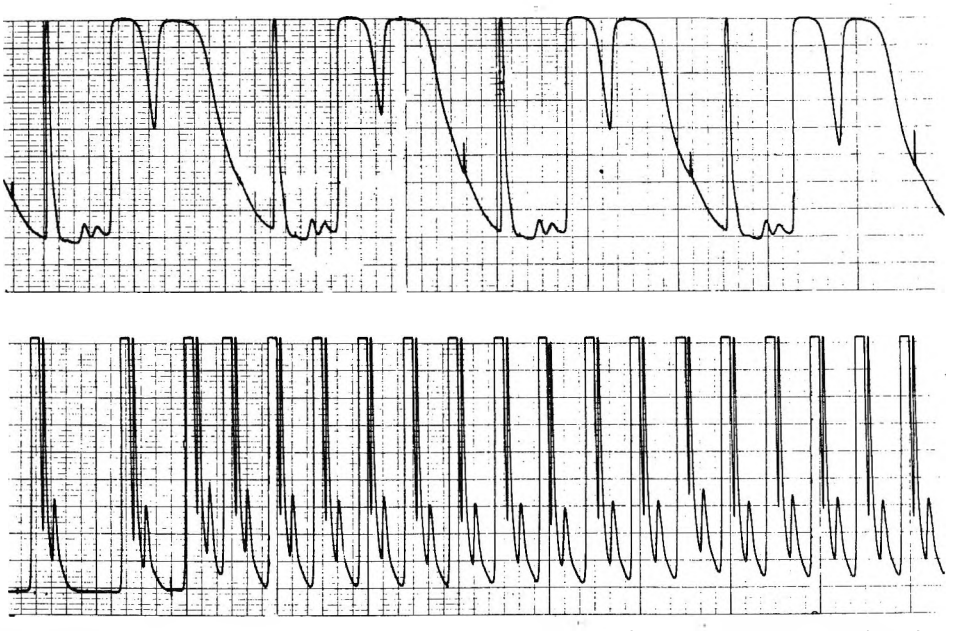

Figure 1. Two representative series of automated repetitive chromatography runs. Absorption at 280 nm is plotted against time. Repetition rate for the upper chromatogram was once per 5 hr. For the lower chromatogram, the final repetition rate was once per hour. Owing to saturation of the ultraviolet monitor, the extent of separation is greater than the recorder trace suggests.

reduces the number of fractions with which one must deal, and minimizes the problem of waste solvent disposal. This extensively tested system has been found to be flexible in application, reliable, and simple to use; consequently, it should prove valuable for the isolation of natural products, the separation of reaction mixtures, and the routine purification of organic compounds.

Although we do not claim that this system provides resolution equal to that of commercial analytical units, it does, in our hands, afford separations equal or superior to those attained by tlc but on a considerably larger scale. One demonstration of the utility of this system is that it has, in our laboratories, made possible the preparative-scale resolution of a variety of chiral alcohols[1] which had resisted resolution through the more usual (and tedious) methods of fractional crystallization of diastereomeric derivatives.

While this system routinely affects the chromatographic separation of 6–10 g of diastereomers/24 hr, in some cases, samples of up to 50 g have been chromatographed in a single pass. Two examples of the repetitive separations provided by the system are shown in Figure 1.

Limitations of the present system when operating in the automatic mode are (a) solvent gradients cannot be employed (although mixed solvents can be used),[2] (b) the compounds being collected must be stable[3] and of low volatility at 100°, and (c) nonvolatile reagents (salts, buffers) cannot be employed in the solvent system. These limitations are a consequence of the reclamation of solvent, and can be avoided if solvent reclamation is foregone.

Figure 2 is a block diagram depicting component lay-out. After initial application of the sample to the column, the sample pump stops and the main pump commences operation. The main pump feeds from a reservoir which is continually refilled with reclaimed solvent. From the pump, the eluting solvent flows through a pressure gauge, a one-way check valve (a part of the sample injection system), the column, a flow cell of short path length, through whichever of the four solenoid selector valves has been selected, and into the corresponding still. The function of the still(s) is to recover solvent from the eluent and to return the solvent to the reservoir. Nonvolatile materials eluted from the column remain in the boiling kettles of the stills. The absorbance of the column eluent is continuously determined, displayed

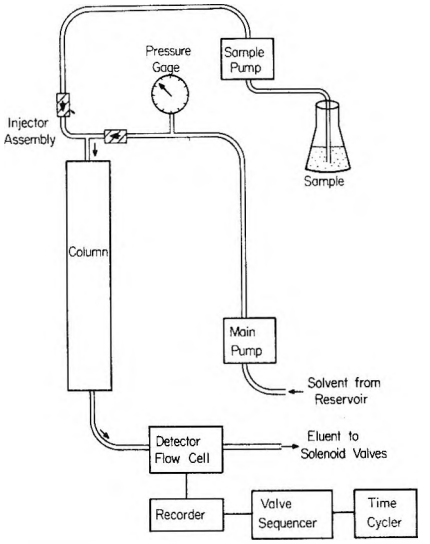

Figure 2. Block diagram of the automated preparative liquid chromatography system.

on the recorder, and monitored at regular short intervals by the valve sequencer unit. This unit, through appropriate circuitry, notes and counts bands of absorbing[4] material as they are eluted, and activates appropriate solenoid selector valves to divert any given band of material into the boiling kettle of the still specified by the settings of the programming switches. The entire band is collected in one kettle since that valve arrangement is maintained until the next band begins to emerge, and is only then changed if the switches are so programmed. With four stills, three chromatographic bands can be separately collected, additional bands being collected in the fourth kettle for discard or rechromatography. Although it is clearly possible to increase the number of stills, situations necessitating the separate collection of more than three fractions have seldom been encountered. When all chromatographic bands have been eluted, the cycle timer stops the main pump and starts the sample pump which introduces a fresh sample onto the column through a one-way valve. Simultaneously, the valve sequencer and the solenoid valve arrangements return to the start position. The main pump resumes action upon

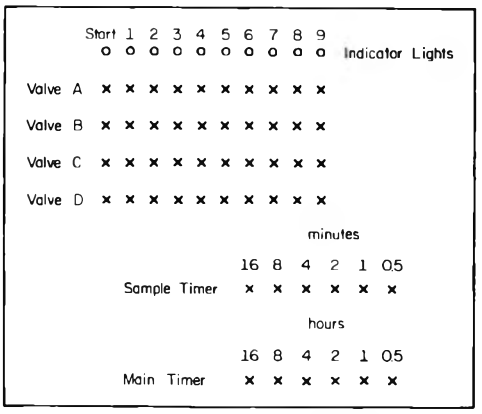

Figure 3. Control panel for the valve sequencer and time cycler units. Each x represents an on–off toggle switch.

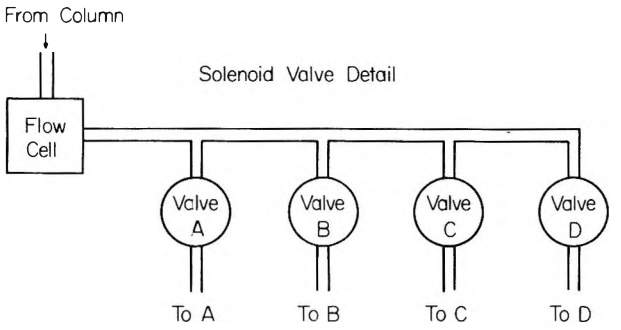

Figure 4. Solenoid valve arrangement for the automated preparative liquid chromatography system. Each valve conducts eluent into the corresponding still.

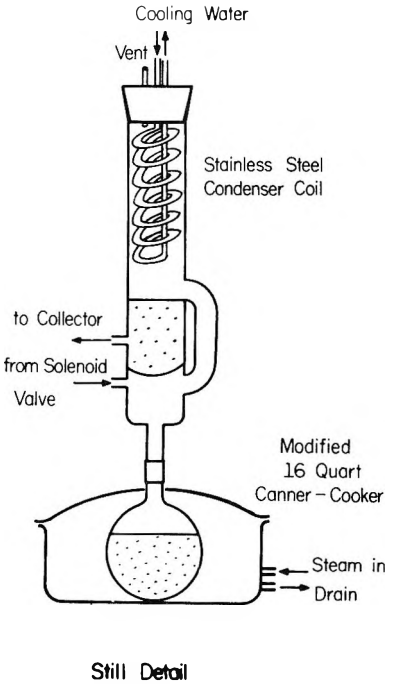

Figure 5. Details of the solvent still and steam heating baths. Four such stills (A–D) are employed.

shutdown of the sample pump. The lengths of the two pump cycles are programmable by switch settings on the timer unit. Figure 3 illustrates the control panels of the valve sequencer and the time cycler units, whereas Figures 4 and 5 illustrate the solenoid valve layout and the solvent still–heating bath arrangement, respectively.

This system employs large commercial or home-built glass chromatography columns holding from 1 to 7 kg of 0.05–0.2 mm silica gel or alumina. These comparatively inexpensive adsorbents are easily packed and allow pressures of less than 30 psig at flow rates of 2.5 l./hr. The low pressures simplify design, operation, and component requirements. Larger columns (12.5 cm diameter, 125 cm length, *ca.* 20 kg of adsorbent) have been fabricated and successfully employed. While larger samples can be accommodated and resolution has been satisfactory, per diem capacity has not been increased by the use of very large columns owing to the pumping rate limitation (2.5 l./hr) of the present main pump. Assuming satisfactory resolution, the principle factor influencing per diem capacity of the system is simply the rate at which solvent can be cycled through the system. Clearly, use of larger columns and greater pumping rates would increase the per diem capacity of the system, although drastic increases in pumping rates will necessitate redesign of the solvent stills.

To assist those who wish to construct similar systems,[5] additional description, circuit diagrams, and dimensioned drawings for chromatography columns have been made available separately as supplemenary material.

Acknowledgment. This work was supported in part by U. S. Public Health Service Grant GM 14518.

Supplementary Material Available. To assist those who wish to construct similar systems,[5] additional description, circuit diagrams, and dimensioned drawings for chromatography columns will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3901.

References and Notes

(1) For a detailed account of this broad-spectrum resolution method, see W. H. Pirkle and M. S. Hoekstra, *J. Org. Chem.*, **39**, 3904 (1974).
(2) Since solvent reclamation is essentially a flash distillation, it is not necessary to use constant boiling mixtures of solvents to avoid changing the solvent composition through fractional distillation from the stills. However, solvent composition might well fluctuate enough to adversely affect detector systems sensing changes in index of refraction.
(3) It should be possible to use a continuous low temperature vacuum evaporation technique to remove solvent from thermally sensitive materials.
(4) While it is not essential that an absorbance detector be employed in the system, the presence of upright and inverted peaks, as might sometimes be afforded by index of refraction or Christenson effect detectors, would constitute a minor problem since the latter would not be counted by the valve sequencer unit. In this event, it would be necessary to include circuitry to automatically reverse the roles of the valve sequencers' positive and negative slope detectors by sensing whether the signal level from the elution detector is greater than or less than that of the base line level.
(5) Almost predictably, the control panel for the sequencer and cycler units arrived from the shop in which it was fabricated bearing the title "Pirkleator No. 1," a name which seems to have taken hold among the users of this system.

An Example of Automated Liquid Chromatography. Synthesis of a Broad-Spectrum Resolving Agent and Resolution of 1-(1-Naphthyl)-2,2,2-trifluoroethanol

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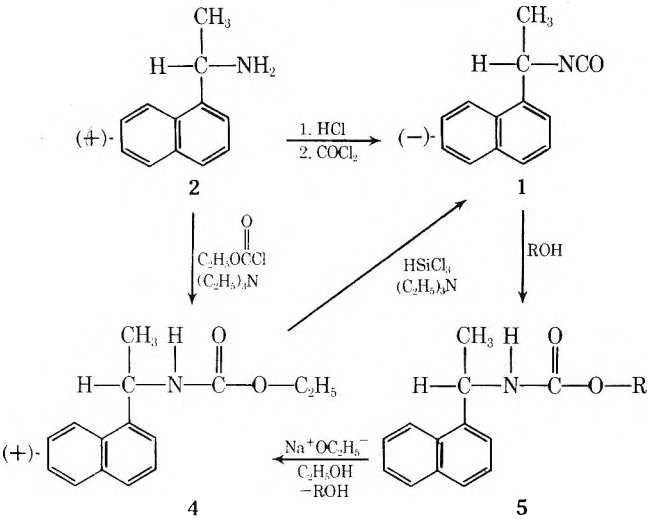
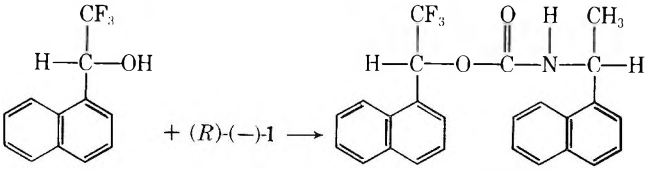
Resolved 1-(1-naphthyl)ethyl isocyanate (1), a useful reagent for the chromatographic resolution, *via* diastereomeric derivatives of a variety of alcohols, α-hydroxy esters, and thiols, can be prepared by the action of phosgene on the hydrochloride of amine **2**, or by treatment of ethyl carbamate **4** of amine **2** with trichlorosilane; however, no **1** is obtained when **4** is treated with trimethylchlorosilane. The diastereomeric carbamates derived from racemic 1-(1-naphthyl)-2,2,2-trifluoroethanol (**3**) and chiral 1-(1-naphthyl)ethyl isocyanate (**1**) are readily separable *via* automated preparative liquid chromatography. Ethanolysis of the separated diastereomers affords both enantiomers of the resolved alcohol and a recoverable form of the resolving agent.

While optical resolutions have frequently been effected *via* chromatographic separation of diastereomeric derivatives, this has seldom been the preferred approach for preparative scale work. Moreover, no chiral derivatizing reagent has previously been recommended for the chromatographic resolution of a broad spectrum of derivatizable enantiomers.[2] Since we have found it possible, on a preparative scale, to separate chromatographically the diastereomeric derivatives (**4**) formed when enantiomeric 1-(1-naphthyl)ethyl isocyanate (**1**) is allowed to react with any of a number of racemic alcohols, α-hydroxy esters, and thiols,[3] and since subsequent hydrolysis of the separated diastereomers can then afford the resolved alcohols or thiols, we report here our evaluation of three synthetic routes to this useful resolving agent, beginning with commercial (*R*)-(+)-1-(1-naphthyl)ethylamine (**2**). Furthermore, we illustrate the use of this reagent in the resolution of 1-(1-naphthyl)-2,2,2-trifluoroethanol (**3**). Resolved fluoro alcohol **3**, considerably more effective as a chiral nmr solvent than the previously used phenyl analog,[4] has until now been obtained with difficulty since conventional methods for its resolution have been tedious and generally unsatisfactory.[5] In addition to being widely applicable, the resolution method illustrated here is convenient, is efficient in terms of material and labor, affords both enantiomers, and regenerates the resolving agent. In combination with a newly developed automated preparative liquid chromatography system,[6] the present method makes feasible the resolution of multigram quantities of numerous alcohols, amines,[7] and thiols. We further point out that most of the diastereomeric carbamates thus far encountered are crystalline after (and sometimes before) separation. In these cases there exists the possibility of separating the diastereomers by fractional crystallization.[8]

Three possible synthetic routes to isocyanate **1** from amine **2** were considered. The analogous preparation of (*R*)-(−)-1-phenylethyl isocyanate by the action of phosgene on the corresponding amine hydrochloride has been reported.[9] In the case of amine **2**, this method affords isocyanate **1** almost quantitatively, the only hindrance being the toxicity of phosgene. The recently reported method of isocyanate synthesis involving treatment of carbamates with trimethylchlorosilane[10] failed to give detectable (nmr) amounts of isocyanate **1** when applied to the ethyl carbamate **4**, prepared by reaction of amine **2** with ethyl chloroformate. However, under similar conditions, trichlorosilane readily converts ethyl carbamate **4** into isocyanate **1**, thereby offering a second route to **1** which avoids phosgene. This second synthesis is of a particular value since, after separation, the diastereomeric carbamates **5** can be cleaved by the action of ethanolic sodium ethoxide into the resolved alcohol and ethyl carbamate **4**. Hence this synthetic scheme offers a convenient means of recovering the resolving agent.



An example of the use of isocyanate **1** as a resolving agent is provided by the resolution of fluoro alcohol **3**. Isocyanate (*R*)-(−)-**1** reacts cleanly with an equimolar quantity of racemic alcohol **3** at 80° to afford a syrupy mixture of the diastereomeric carbamates (**5a** and **5b**) which is readily separable by chromatography on alumina with benzene, provided the ratio of alumina to carbamate is 2500:1 or greater. Chromatography of 1-g portions of this mixture with benzene on a 2.5 in. × 48 in. column of acidic alumina cleanly separates the diastereomers (α 1.37) as determined by absorbance monitoring at 280 nm. Using the system described,[6] 6–10 g of the diastereomeric mixture may be separated per 24-hr period.[11] Figure 1 illustrates the repetitive chromatographic separation of diastereomeric carbamates **5a** and **5b**.



The *R,R* diastereomer is eluted first and both diastereomers are, once separated, readily recrystallized from hexane. Treatment of either diastereomer with ethanolic sodium ethoxide cleanly liberates chiral fluoro alcohol **3** and affords ethyl *N*-(1-[1-naphthyl]ethyl)carbamate (**4**) which is easily separable from **3** and is reconvertible to isocyanate **1**.

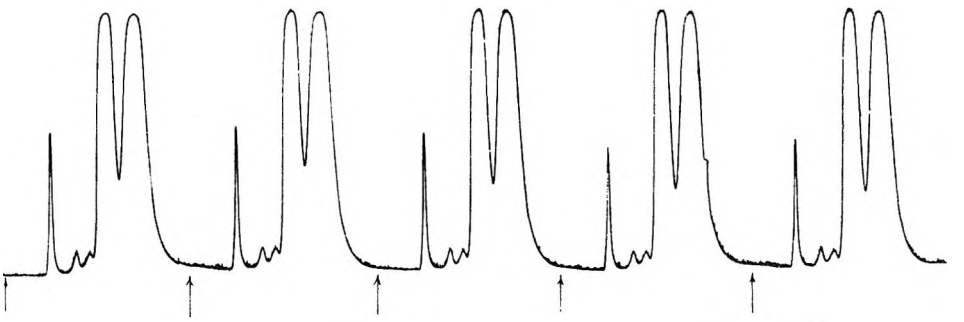


Figure 1. The automated repetitive chromatographic separation of diastereomeric carbamates **5a** and **5b** on acidic alumina with benzene. The separability factor, α, is 1.37. The *R,R* diastereomer **5a** is the first of the two major bands; minor absorptions are caused by impurities. Sample injections of 1 g (arrows) occur every 3 hr. Because of saturation of the 280-nm detector, the extent of peak overlap appears to be greater than is actually the case.

Experimental Section

Melting points were taken on a Büchi apparatus and are uncorrected. Optical rotations were determined at 589 nm in a Zeiss visual polarimeter, using a 1.0-dm tube. Infrared spectra were measured with a Perkin-Elmer 521 or a Perkin-Elmer 237B spectrophotometer. Nmr spectra were obtained with a Varian A-60-D spectrometer. Mass spectra were determined by J. C. Cooke and his associates, using a Varian MAT CH-5 spectrometer. Microanalyses were performed by J. Nemeth and his colleagues.

(*R*)-(+)-1-(1-Naphthyl)ethylamine (2). Resolved material having a rotation $\alpha^{28.5}$ +80.47 ± 0.05° (neat, l = 1) was obtained from Norse Chemical Co., and was used without further purification.

(*R*)-(−)-1-(1-Naphthyl)ethyl Isocyanate (1). A. Phosgene Method. In a 1000-ml three-necked flask fitted with a reflux condenser, mechanical stirrer, and gas inlet tube, amine (*R*)-(+)-2 (17.13 g, 0.10 mol) was dissolved in dry toluene (200 ml). The solution was stirred, and dry hydrogen chloride was added through the inlet tube, which was placed with the opening above the liquid level, to prevent plugging. After most of the white, solid 1-(1-naphthyl)ethylamine hydrochloride had formed, the inlet tube was lowered into the mixture and more hydrogen chloride was added to assure that the solution was saturated. Additional dry toluene (100 ml) was added, and phosgene was slowly and continuously bubbled into the mixture, which, after a few minutes, was heated to reflux for 4 hr. At this point all solid had disappeared, leaving a straw-colored solution. The toluene was distilled at reduced pressure, the residual liquid was transferred to a 100-ml flask and distilled to afford colorless isocyanate (*R*)-(−)-1 (19.02 g, 96.3%): bp 106–108° (0.16 mm); $[\alpha]^{24.1}$ −50.5 ± 0.2° (c 27.9, benzene); ir (neat) 2260 (N=C=O), 795, and 775 cm^{-1}; nmr ($CDCl_3$) δ 1.60 (d, 3, J = 6.7 Hz, CH_3), 5.38 (quartet, 1, J = 6.7 Hz, CH), and 7.21–8.04 ppm (m, 7, $C_{10}H_7$); mass spectrum (70 eV) *m/e* (rel intensity) 197 (71, M^+), 182 (100), 155 (40), 154 (13), 128 (21), 127 (35).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.03; H, 5.66; N, 6.95.

B. Trichlorosilane Method. To a stirred solution of ethyl carbamate (*R*)-(+)-4 (24.33 g, 0.10 mol) and triethylamine (11.13 g, 0.11 mol) in dry benzene (200 ml), a solution of trichlorosilane (14.90 g, 0.11 mol) in dry benzene (50 ml) was added dropwise, over a 15-min period. After 30 min, the solution was heated to reflux for 30 min, allowed to cool to room temperature, and filtered under nitrogen to remove triethylamine hydrochloride. Removal of the solvent at reduced pressure left a cloudy yellow liquid, which was distilled under vacuum to give isocyanate (*R*)-(−)-1 (16.4–16.7 g, 83.1–84.6%), identical by nmr and ir with that prepared by the phosgene method, $[\alpha]^{23.4}$D −50.8 ± 0.5° (c 32.9, benzene).

The preparation of isocyanate 1 from amine 2 using the trichlorosilane sequence may be carried out without isolation of the intermediate ethyl carbamate 4; the overall yield is not substantially altered. Thus into a stirred solution of amine (*R*)-(+)-2 (17.12 g, 0.10 mol) and triethylamine (11.13 g, 0.11 mol) was rapidly poured a solution of ethyl chloroformate (12.28 g of 97%, 0.11 mol) in dry benzene (50 ml). The mixture was stirred for 30 min, heated to reflux for 30 min, and allowed to cool. Filtration under nitrogen to remove triethylamine hydrochloride gave a clear yellow solution to which additional triethylamine (11.13 g, 0.11 mol) was added. The solution was stirred, and a solution of trichlorosilane (14.90 g, 0.11 mol) in dry benzene (50 ml) was added dropwise over a 15-min period. After a 30-min period, the solution was heated to reflux for 30 min, then allowed to cool to room temperature, and filtered under nitrogen to remove triethylamine hydrochloride. Removal of the solvent at reduced pressure left a brown liquid sometimes containing a solid which was removed by filtration after dissolving the isocyanate in dry pentane. After pentane removal, vacumm distillation gave isocyanate (*R*)-(−)-1 (14.07 g, 71.4%).

(*R*)-(+)-Ethyl *N*-(-[1-Naphthyl]ethyl)carbamate (4). Into a stirred solution of amine (*R*)-(+)-2 (17.12 g, 0.10 mol) and triethylamine (11.13 g, 0.11 mol) in dry benzene (150 ml) was rapidly poured a solution of ethyl chloroformate (12.28 g of 97%, 0.11 mol) in dry benzene (50 ml). After stirring for 30 min, the mixture was heated to reflux for 30 min, then allowed to cool. The mixture was then filtered to remove triethylamine hydrochloride, and concentrated at reduced pressure to afford crude crystalline 4 (24.4 g). Recrystallization from benzene–petroleum ether affords ethyl carbamate (*R*)-(+)-4 (20.63 g, 84.8%): mp 99.9–100.3°; $[\alpha]^{23}$D +22.7 ± 0.1° (c 19.9, chloroform); ir (KBr) 3325 (NH), 1683 (C=O), 1546, 1258, 1059, 788, and 769 cm^{-1}; nmr ($CDCl_3$) δ 1.18 (t, 3, CH_2CH_3), 1.61 (d, 3, $CHCH_3$), 4.10 (quartet, 2, CH_2CH_3), 5.06 (d, broad, 1, NH) 5.63 (d of quartet, 1, NH-C*H*-CH_3) and 7.20–8.20 ppm (m, 7, $C_{10}H_7$).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found C, 74.33; H, 7.11; N, 6.05.

***dl*-1-(1-Naphthyl)-2,2,2-trifluoroethanol (3).** A solution of lithium trifluoroacetate, prepared by addition of lithium hydride (8.0 g, 1.0 mol) to trifluoroacetic acid (101 g, 0.89 mol) in dry tetrahydrofuran (200 ml), was added over a 10-min period to the Grignard reagent prepared from 1-bromonaphthalene (207 g, 1.0 mol) and magnesium turnings (25 g, 1.0 mol) in dry ether (950 ml). After a 1-hr reflux period, 6 *M* hydrochloric acid was added with cooling until the mixture was acidic, and the organic layer was collected after addition of pentane (500 ml). The crude 1-naphthyl trifluoromethyl ketone (243 g), isolated by solvent evaporation, was not purified, but was mixed with methanol (200 ml) and reduced by portionwise addition of sodium borohydride (12 g, 0.32 mol). This solution was diluted with water (1000 ml), acidified with hydrochloric acid, and twice extracted with 200-ml portions of methylene chloride. The solvent was removed at reduced pressure and the residual oil was dissolved in a solution of potassium hydroxide in aqueous methanol (prepared from 260 g of potassium hydroxide, 160 ml of water, and 1440 ml of methanol). The resulting solution (in which the desired fluoro alcohol 3 is present in anionic form) was extracted several times with 200-ml portions of pentane in order to remove naphthalene and binaphthyl. The bulk of the methanol was removed at reduced pressure, water (1000 ml) was added, and the resulting solution was acidified with 12 *M* hydrochloric acid. Extraction with three 200-ml portions of methylene chloride, drying of the extracts, and removal of the solvent at reduced pressure, followed by distillation of the resulting oil, gave *dl*-3, which solidified in the receiving flask (116 g, 0.51 mol, 58%): bp 83–85° (0.025 mm); mp 47.4–48.5° (recrystallized from hexane); ir (neat liquid) 3410 (OH), 1270, 1165, 1120, 795, and 780 cm^{-1}; nmr ($CDCl_3$) δ 3.24 (s, 1, OH), 5.62 (quartet, 1, CH), and 7.16–7.96 ppm (m, 7, $C_{10}H_7$); mass spectrum (70 eV) *m/e* (rel intensity) 226 (40, M^+), 157 (80, $[M - CF_3]^+$), 129 (100), 128 (54), 127 (38).

Anal. Calcd for $C_{12}H_9F_3O$: C, 63.72; H, 4.01. Found: C, 63.77; H, 3.98.

1-(1-Naphthyl)-2,2,2-trifluoroethyl *N*-(1-[1-Naphthyl]ethyl)carbamate (5a, 5b). Racemic fluoro alcohol 3 (6.20 g, 0.27 mol) and isocyanate (*R*)-(−)-1 (5.34 g, 0.27 mol) were mixed and heated to 80° while protected by a drying tube, for 65 hr,[12] by which time the isocyanate band at 2260 cm^{-1} had disappeared. The mixture

was then automatically chromatographed with benzene on a 2.5 × 48 in. column of Brinkmann acidic alumina. The effluent was monitored at 280 nm.

The first major fraction to be eluted was (*R,R*)-(+)-**5a** (4.34 g, 0.010 mol, 75.0%). Recrystallization from hexane gave white needles: mp 139.7–140.6°; ir (KBr) 3325 (NH), 1728, 1696, 1532, 1514, 1270, 1242, 1183, 1174, 1064, 801, and 779 cm^{-1}; nmr ($CDCl_3$) δ 1.54 (d, 3 $CHCH_3$), 5.48 (s, 1, NH), 5.54 (quartet, 1, $CHCH_3$), 7.03 (quartet, 1, $CHCF_3$), and 7.16–8.28 ppm (m, 14, both $C_{10}H_7$); $[\alpha]^{26.7}D$ +56.1 ± 1.1° (c 3.65, chloroform).

Anal. Calcd for $C_{25}H_{20}F_3NO_2$: C, 70.91; H, 4.76; N, 3.31. Found: C, 70.78; H, 4.77; N, 3.47.

The second major fraction to be eluted was (*S,R*)-(−)-**5b** (5.62, 0.013 mol, 97.0%), which can be recrystallized from hexane: mp 123.1–124.0°; ir 3450 (NH) 1724, 1505, 1264, 1232, 1180, 1167, 1127, 1061, 790, and 769 cm^{-1}; nmr ($CDCl_3$) δ 1.46 (d, 3, $CHCH_3$), 5.55 (s, 1, NH) 5.58 (quartet, 1, $CHCH_3$), 7.02 (quartet, 1, $CHCF_3$), and 7.20–8.28 ppm (m, 14, both $C_{10}H_7$); $[\alpha]^{24.5}D$ −12.2 ± 0.3° (c 15.5, chloroform).

Anal. Calcd for $C_{25}H_{20}F_3NO_2$: C, 70.91; H, 4.76; N, 3.31. Found: C, 71.05; H, 4.78; N, 3.41.

Conversion of (*R,R*)-(+)-1-(1-Naphthyl)-2,2,2-trifluoroethyl *N*-(1-[1-Naphthyl]ethyl)carbamate (5a) to (*R*)-(−)-(1-Naphthyl)-2,2,2-trifluoroethanol (3). Carbamate (*R,R*)-(+)-**5a** (4.23 g, 0.01 mol) was added to a solution of ethanolic sodium ethoxide (2.5 g sodium in 30 ml of ethanol) and refluxed for 30 min, at which time tlc (silica gel–methylene chloride) showed no remaining **5a**. The ethanol was removed at reduced pressure and excess base was neutralized with dilute hydrochloric acid. The aqueous mixture was extracted with three 50-ml portions of methylene chloride and the combined extracts were dried, concentrated, and chromatographed automatically with methylene chloride on a 2.5 × 48 in. column of Brinkmann silica gel.

The first major band to be eluted was fluoro alcohol[13] (*R*)-(−)-**3** (2.17 g, 0.0096 mol, 95.7%) identical by nmr, ir, and tlc to racemic **3**. Molecular distillation gave a waxy solid: mp 51.6–53.2°; $[\alpha]^{25.3}D$ −25.7 ± 0.7° (c 5.1, ethanol).

The second fraction contained, upon removal of the solvent, (*R*)-(+)-ethyl *N*-(1-[1-naphthyl]ethyl)carbamate (2.02 g, 0.0083 mol, 83.1%), identified by nmr.

A similar hydrolysis of carbamate (*S,R*)-(−)-**5b** gave, after chromatography, fluoro alcohol (*S*)-(+)-**3**: mp 51.6–53.6°; $[\alpha]^{25.7}D$ +25.8 ± 0.5° (c 5.1, ethanol).

Acknowledgements. This work was supported by the National Institute of Health through Research Grant GM 14518. The mass spectral data processing equipment employed was provided by National Institutes of Health Grants CA 11388 and GM 16864, from the National Cancer Institute, and the National Institute of General Medical Sciences.

Registry No.—(*R*)-**1**, 42340-98-7; (*R*)-**2**, 3886-70-2; *dl*-**3**, 17556-44-4; (*R*)-**3**, 22038-90-0; (*S*)-**3**, 33758-06-4; (*R*)-**4**, 53043-11-1; (*R,R*)-**5a**, 53043-12-2; (*S,R*)-**5b**, 53043-13-3; trifluoroacetic acid, 76-05-1; 1-bromonaphthalene, 90-11-9.

References and Notes

(1) (a) Alfred P. Sloan Foundation Research Fellow, 1970–1974. (b) Phillips Petroleum Predoctoral Fellow, 1972–1974.
(2) In view of the widespread separability of the diastereomeric derivatives of **1**, it is clear that this reagent, in conjunction with a high-pressure analytical liquid chromatography system, offers a useful tool for the determination of optical purity of those enantiomeric compounds which form derivatives with **1**.
(3) While a more comprehensive report of this resolution method will appear later, a partial list of compounds whose diastereomeric derivatives with **1** have been separated chromatographically on a preparative scale is as follows: 1-phenyl-2,2,2-trifluoroethanol; 1-phenyl-2,2,2-trichloroethanol; 1-phenyl-2,2,2-tribromoethanol; 1-(1-naphthyl)-2,2,2-trifluoroethanol; 1-(2-naphthyl-2,2,2-trifluoroethanol; 1-(3-pyrenyl)-2,2,2-trifluoroethanol; 1-(9-anthryl)-2,2,2-trifluoroethanol; 1-(10-methyl-9-anthryl)-2,2,2-trifluoroethanol; 1-phenyl-2,2,3,3,4,4,4-heptafluoro-1-butanol; 1-phenylethanol; 1-(4-nitrophenyl)ethanol; 1-(4-methoxyphenyl)ethanol; 1-(1-naphthyl)ethanol; 1-(2-naphthyl)ethanol; 1-phenylethanethiol; ethyl 2-mercaptopropanoate; methyl 2-hydroxy-3,3-dimethylbutanoate; methyl mandelate; 1-cyclohexyl-2,2,2-trifluoroethanol; 3-hydroxy-3-phenyl-4,4,4-trifluoro-1-butyne.
(4) W. H. Pirkle, R. L. Muntz, and I. C. Paul, *J. Amer. Chem. Soc.*, **93**, 2817 (1971), and references therein.
(5) R. L. Muntz, Ph.D. Thesis, University of Illinois, Urbana, 1972.
(6) W. H. Pirkle and R. W. Anderson, *J. Org. Chem.*, **39**, 3901 (1974).
(7) The use of racemic isocyanates and chiral alcohols or, alternatively, racemic amines and chiral chloroformates, will afford diastereomeric carbamates which may be separated and hydrolyzed.
(8) The phenyl analog of this isocyanate, commercially available for several years, has previously been used [H. W. Gschwend, *J. Amer. Chem. Soc.*, **94**, 8430 (1972)] to afford diastereomers separable by crystallization. We are unaware of prior examples of chromatographic separation of diastereomeric carbamates derived from 1-phenylethyl isocyanate. In point of fact, we have found that the diastereomeric carbamates of this isocyanate do not, in general, separate as well chromatographically as those derived from **1**.
(9) T. L. Cairns, *J. Amer. Chem. Soc.*, **63**, 871 (1941).
(10) G. Greber and H. R. Kricheldorf, *Angew. Chem.*, **80**, 1028 (1968).
(11) In the event unreacted alcohol or other strongly retained materials are present in the crude product, a rough large-scale prechromatography may be desirable.
(12) Use of 1% of either *N,N*-dimethylethanolamine or di-*n*-butyltin dilaurate as a catalyst reduces reaction times to as little as ca. 10 hr.
(13) The absolute configuration of fluoro alcohol **3** has been established previously by the chiral nmr solvent method, using a partially resolved sample. See W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **89**, 5485 (1967). Subsequent work in these laboratories further supports the assignment.

Base-Catalyzed Decomposition of 1,2,3-Selenadiazoles and Acid-Catalyzed Formation of Diselenafulvenes

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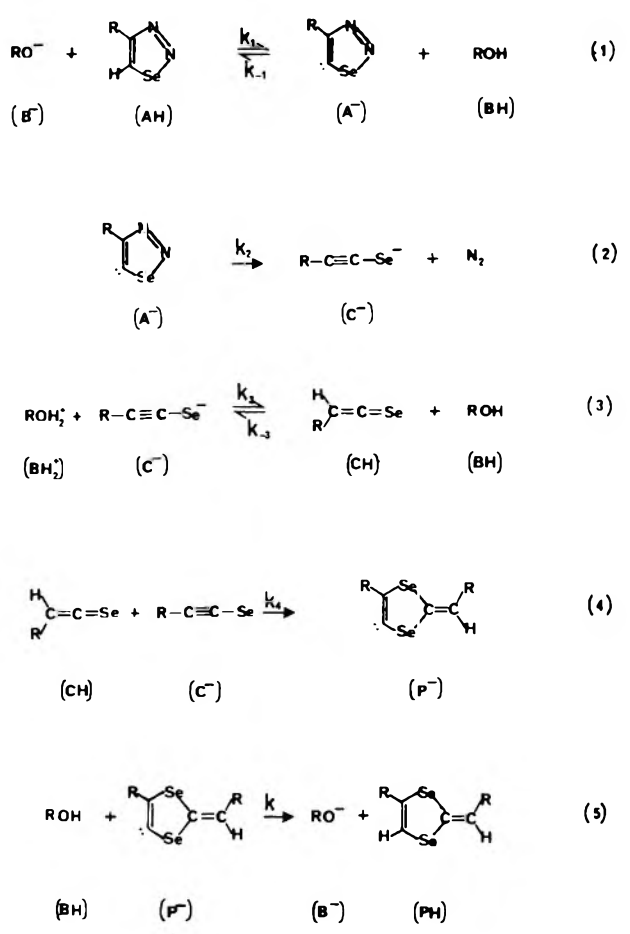
The kinetics and mechanism of the base-catalyzed decomposition of 4-aryl-1,2,3-selenadiazole with arylethynylselenolate ion as the intermediate and the subsequent hydrogen ion catalyzed formation of substituted 1,3-diselenafulvenes from this intermediate in basic alcoholic media have been investigated. Details of the mechanism, rate constants, and dependence upon the acidity function H_- are reported and discussed. An interesting coupling of the various steps in the above processes under certain conditions has been found and analyzed in some detail.

The mechanism of the formation of the 1,3-diselenafulvenes has previously been reported.[2] The steps of this reaction can be summarized as in Scheme I.

While Scheme I, deduced from our experimental observations, adequately describes the results, several points remained to be clarified. These were (a) the importance of the equilibrium in step 1 as opposed to an irreversible and concerted hydrogen abstraction–decomposition to the ethynylselenolate ion, and (b) the extent of the equilibrium in step 3 and thus a measure of the stability of the heretofore unknown selenaketene. By undertaking a kinetic study of the reaction we hoped to gain a better understanding of the

Scheme I



above as well as to find the kinetic interrelationships of this interesting and complex five-step reaction sequence in which the first step is base and some of the subsequent steps are acid catalyzed.

Furthermore, in line with the existing interest in testing the significance and validity of acidity scales in the acid- or base-catalyzed reactions of heterocyclic compounds kinetically,[3] we hoped to find a correlation of our results with the H_- scale. In this paper we wish to report our progress in the study of the above reaction.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Model T-60 Varian spectrometer. Mass spectra were obtained on a Model CH5 Varian spectrometer. Ultraviolet spectra were obtained on a Pye-Unicam SP-800 using the automatic repeat scanning facility. Melting points were determined on a Kofler hot stage. Elementary analysis was performed by Mikroanalytisches Laboratorium Dornis u. Kolbe, West Germany.

All the alcohols used were dried by refluxing over an appropriate metal alkoxide before use. The alkoxide solutions used for kinetic measurements were prepared by adding potassium metal to the respective alcohol under nitrogen.

Kinetic experiments involving volumetric gas measurements were performed using a Warburg type respirometer, Gilson Model GR14, with 14 reaction vessels. The experiments were performed as follows. From a stock solution of the selenadiazole in the appropriate solvent (typical concentration of about 60 mg/10 ml), 0.5 ml was pipeted into the side arm of a Warburg flask, and 1.5 ml of the base solution was pipeted into the main reaction compartment. The flasks were mounted on the respirometer and the apparatus was allowed to reach equilibrium for about 45 min. To start each reaction, the corresponding flask was removed from the temperature bath, its contents were rapidly mixed, and it was replaced before a lapse of about 30 sec. Readings were taken on the verniered volumeter until no appreciable gas evolution took place.

Spectrophotometric kinetic measurements were carried out by adding sufficient potassium phenylethynylselenolate to about 3 ml of the respective solvent to give a maximum absorption peak on the recorder when using a 1-mm cell. Measurements were taken at 308 and 340 nm.

The preparation of the selenadiazoles and their conversion into the 1,3-diselenafulvenes were carried out as previously described.[2,4]

ω-d_3-Acetophenone. Phenylacetylene, 3.0 g (0.03 mol), was added to a solution of 3 ml of deuterium oxide containing about 0.1 g of metallic sodium and stirred magnetically for 1 hr at room temperature. Concentrated deuteriosulfuric acid (98%), 5 ml, and 0.5 g of mercuric sulfate were mixed and the stirring was continued for 0.5 hr (until the liquid layer became homogeneous). The solution was filtered through a sintered glass funnel and washed with 2 ml of water, and the filtrate was extracted several times with ether. The combined ether layer was evaporated to give 3.2 g of an oil. The nmr spectrum of this oil showed only aromatic protons.

4-Phenyl-5-*d*-1,2,3-selenadiazole. The ω-d_3-acetophenone obtained in the previous preparation was converted without further purification to its semicarbazone derivative in the usual manner. The dried semicarbazone, 4.1 g (23.2 mmol), was dissolved in 10 ml of glacial acetic acid and 2.6 g (23.4 mmol) of finely powdered selenium dioxide was added and the solution heated with occasional shaking on a water bath for 1 hr. The solution was filtered hot to remove the deposited selenium and water was added to the main filtrate until turbid. The reddish-brown solid that separated upon cooling was dissolved in 40 ml of ethanol, decolorized with activated charcoal, and crystallized by the addition of water. A pure material was obtained after several recrystallizations, 3.4 g (53% yield based on the phenylacetylene used), mp 76°. Mass spectrum showed 95% deuterium content in the 102/103 fragment (Ph—C≡C—H^+).

Potassium Phenylethynylselenolate. Clean metallic potassium, 1.5 g, was added to a solution of 6 ml of absolute ethanol in 50 ml of dry dioxane. After the evolution of hydrogen gas ceased, the solution was filtered in a dry N_2 atmosphere. Freshly recrystallized selenadiazole, 0.1–0.2 g, was added to 5-ml aliquots of the above solution in centrifuge tubes. After N_2 gas evolution ceased, the precipitate was centrifuged and the supernatant decanted, and the solid was washed several times with dry ether, dried, and kept under desiccation. Typical analysis for several preparations were as follows.

Anal. Calcd for C_8H_5KSe: C, 43.83; H, 2.28; K, 17.90; Se, 36.05. Found: (a) C, 44.60; H, 4.73; K, 13.05; Se, 26.75; (b) C, 42.10; H, 4.80; K, 10.38; Se, 21.33; (c) C, 38.40; H, 3.39; K, 7.30; Se, 29.76.

The molar absorption of the potassium phenylethynylselenolate was obtained in the following way. Selenolate salt (2.0 mg) was dissolved in 10 ml of concentrated ethanolic base solution and absorption at 308 nm, its λ_{max}, was obtained. Subsequently another 2.0 mg of the salt was dissolved in 10 ml of ethanol and allowed to stand and react to form the 1,3-diselenafulvene derivative. From the ultraviolet spectrum of the resulting solution, the concentration of the pure potassium phenylethynylselenolate salt in the salt mixture was determined by measuring the optical absorption of the salt mixture at 340 nm. From several such determinations the average molar absorption of the pure potassium selenolate was determined to be 2.05×10^5.

Kinetics of Deuterium Exchange at C-5 of 4-Phenyl-5-*d*-1,2,3-selenadiazole. 4-Phenyl-5-*d*-1,2,3-selenadiazole, 36 mg, was added to 3 ml of a 4×10^{-3} *M* solution of metallic potassium in ethanol at 22°. Aliquotes, 0.2 ml, were removed at appropriate time intervals and the reaction was quenched by adding the aliquotes to test tubes containing two drops of glacial acetic acid. The solvents were evaporated and the mass spectrum of the residue was obtained. The ratios of the fragment peaks at 102 and 103 were measured.

Kinetics of Deuterium Exchange at C-5 Position of 4-Phenyl-5*H*-1,2,3-selenadiazole in 1-Deuterioethanol. The same procedure as above was employed using 5*H*-selenadiazole and 1-deuterioethanol of 75% deuterium enrichment.

Measurement of the Acidity Function. H_- values of the various reaction media used were measured according to the method described by Schaal and Gadet.[5]

Results and Discussion

Kinetics of the reaction pathway shown in Scheme I were first studied in two separate stages as described below.

Part I. The decomposition of 4-phenyl-1,2,3-selenadiazole (AH) and production of the phenylethynylselenolate ion (C^-), steps 1 and 2, were studied under conditions of

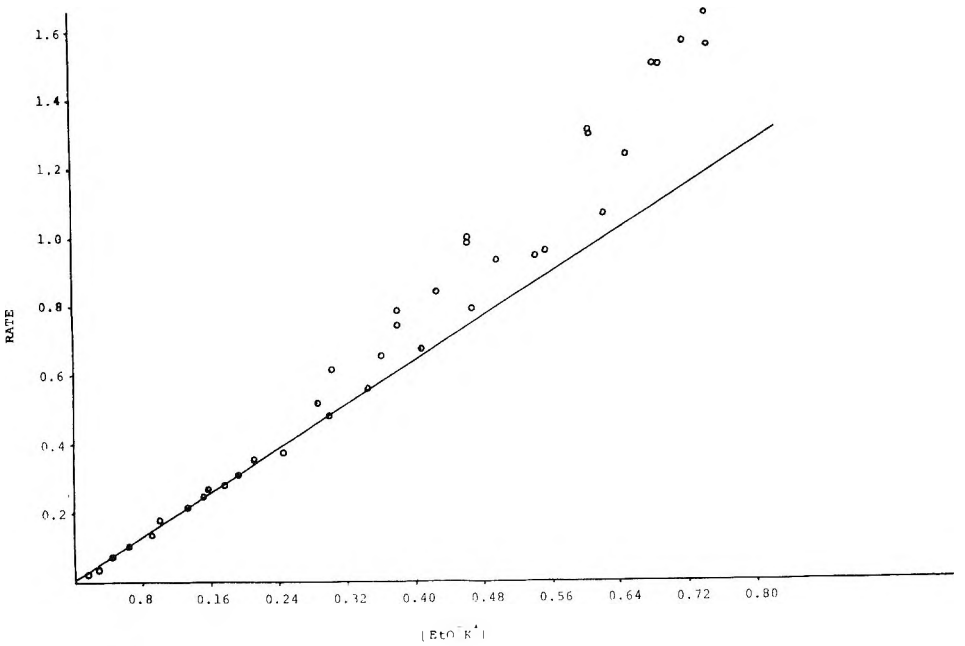


Figure 1. Observed rate *vs.* $[B^-]_0$ in ethanol at 32°.

constant basicity. This condition was realized in basic ethanolic solutions, where either the basicity of the medium was so low that the production of PH from C^- [steps 3, 4, and 5] occurred almost instantaneously thereby regenerating the consumed base and maintaining a constant base concentration, or the basicity was so high that the consumption of B^- in step 1 did not appreciably reduce the base concentration of the medium throughout the reaction. Pseudo-first-order rate constants were obtained from the following rate law[6a]

$$\log \frac{V_\infty - V_t}{V_\infty} = \frac{r}{2.303} t \qquad (6)$$

where $r = [B^-]_0 k_1 k_2 / k_{-1}'$, $k_{-1}' = k_{-1}[BH]$, $[B^-]_0$ = initial base concentration, and V_t and V_∞ are volumes of the N_2 gas evolved at time t and at the completion of the reaction, respectively. Equation 6 is obtained by assuming a fast equilibrium for step 1 and steady state condition for $[A^-]$. All experiments showed a smaller rate within the first 30 sec of the reaction. Analysis has shown that this time is substantially independent of the base concentration and is probably due to the time needed for the homogenization of the solution and equilibration of the measuring apparatus. This "time lag" therefore seems to be caused by physical conditions and not by a kinetic "build-up" period which would necessarily show a base dependence.

A plot of r *vs.* $[B^-]$ for base concentrations up to about 0.23 M gave a straight line, the slope of which determines $k_1 k_2 / k_{-1}'$ to be 1.6 ± 0.1 M^{-1} min^{-1}. At higher base concentrations (Figure 1), r deviates upward, indicating an increase in lyate ion activity of the base.[7a] This enhancement of the lyate ion activity at high base concentration is expected, and it is attributed to a decrease in the solvent's ability to solvate. Bowden and others,[7b] however, have pointed to the fact that this increase in lyate ion activity is already appreciable at 0.1 M ethoxide concentrations, making it necessary to apply eq 7 below for the calculation of the basic strength of the solution in this region.

$$H_- = \text{const} + \log [OR^-] \qquad (7)$$

We therefore constructed an H_- scale for the region of base concentration used in this work. Figure 2 shows a plot of log $[EtO^-K^+]$ *vs.* H_- for our range of base concentrations. It can be seen that with the accuracy of the data points, a straight line of unit slope can be drawn up to a base concentration of about 0.3 M. Above this concentration, eq 7 does not seem to hold. It should be noted that our H_- values are consistently slightly higher than those reported in Bowden's review. However, such a shift has no influence on our conclusions concerning the linear relations involving H_-.

Assuming, as usual, a similarity between the indicator acid (substituted nitroanilines) and AH in strongly basic solutions, a linear relationship between log r and H_- is expected. Figure 3 shows such a plot. Although at low basicity a reasonably straight line with a near unit slope can be drawn, the linearity breaks down at higher H_- values. Interestingly, the breakdown occurs roughly at the same point as in the plot of log $[B^-]$ *vs.* H_- (Figure 2). However, when, as discussed by More O'Farrall,[8] our data are treated according to its linear free energy relationship with logarithm of the apparent rate, a straight line with a slope of about 0.53 is obtained as shown in Figure 4. Our results thus confirm the usefulness of the extension of the Bunnet and Olsen[9] approach for concentrated basic alcoholic solutions.

To further investigate the relative rates of steps 1 and 2, 4-phenyl-5-*d*-1,2,3-selenadiazole (AD) was used as a substrate. No change in the overall rate was observed, indicating a rapid and complete isotopic exchange before any gas evolution could take place. The isotopic exchange rates of AD and AH in [1-^{1}H]ethanol and [1-^{2}H]ethanol, respectively, were followed mass spectroscopically by measuring the relative peak heights of the 102 and 103, $[PhC{\equiv}CH]^+$ and $[PhC{\equiv}CD]^+$, fragment ions.[10] These experiments were carried out at a base concentration of about 0.004 M. As stated above, the amount of gas evolution [step 2] was negligible during the period of exchange. It was observed that isotopic exchange at 32° for both AD and AH was completed in less than 1 min. The fact that the reverse rate of step 1 is much larger than the forward rate (which follows from a rapid exchange) implies that the rate of the exchange reaction is given by $k_1 [B^-]_0$. Thus k_{1H} and k_{1D} were determined. Although experimental difficulties severely limited the accuracy of the measurements, the rough results obtained are $k_{1H} = 4 \times 10^2\ M^{-1}$ min^{-1}, and $k_{1D} = 2 \times 10^2\ M^{-1}$ min^{-1}.

The reactions of steps 1 and 2 were further investigated by comparing the rates of the decomposition of selenadia-

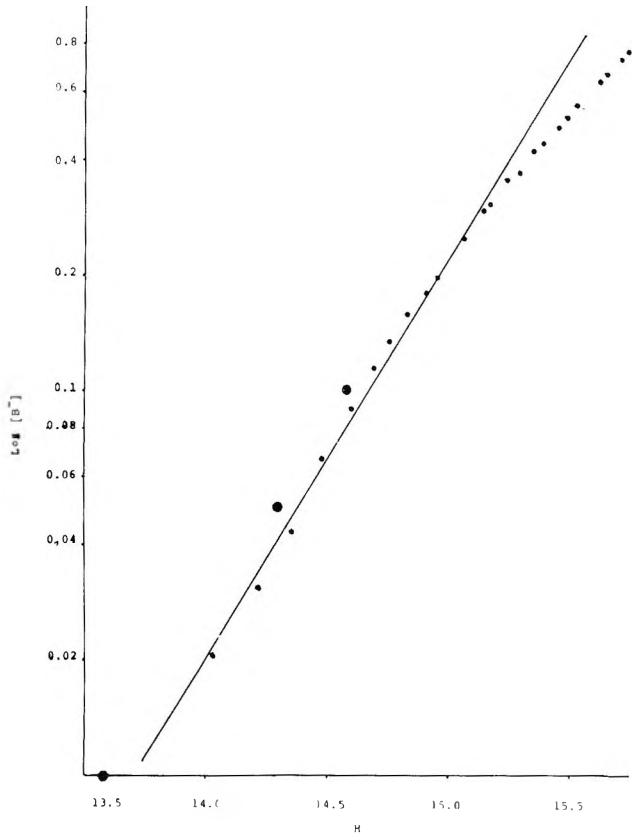


Figure 2. Logarithm of $[EtO^-]$ *vs.* H_-; ·, our values, ●, from Bowden's review.[7]

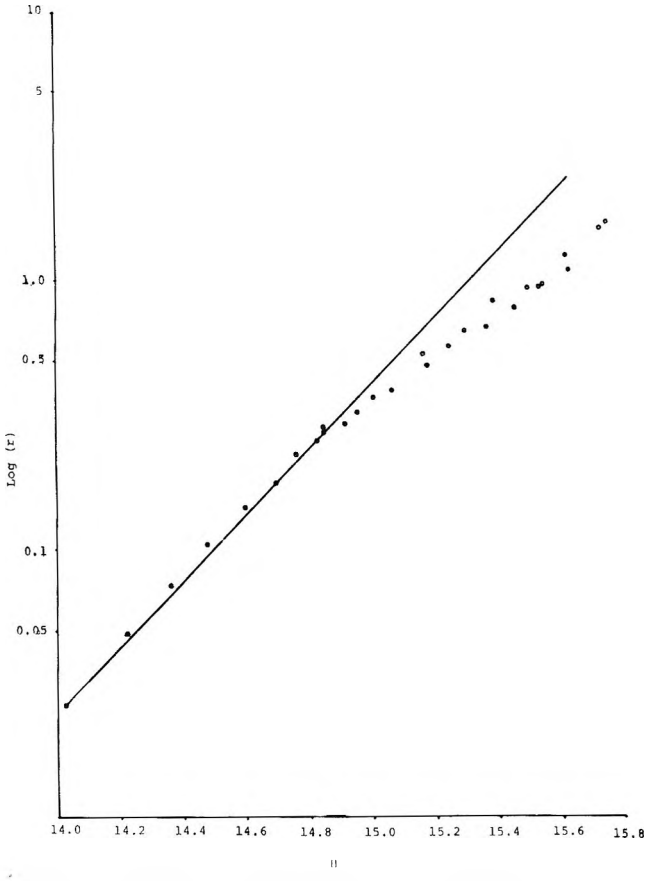


Figure 3. Logarithm of observed rate *vs.* H_- in ethanol.

zoles having substituents on the phenyl ring. The results, shown in Figure 5, indicate a positive ρ value of 2.4. Since isotopic exchange measurements show that step 2 is slower than the reverse direction of step 1, the relatively large positive ρ value observed could be interpreted in either of the following ways: (a) the substituents do not affect the rate of step 2, rather they shift the equilibrium to the right, thereby increasing the steady state concentration of A^- and enhancing the overall rate; (b) they act on the slower unimolecular decomposition step.

Of the two mechanisms which can be envisaged for the decomposition of A^- (Scheme II), one would not expect that in the transition state of (a) the substituents would exert any electronic effects. Hence a ρ value of zero would be expected.[11] However, since electron delocalization away from the heterocyclic ring in (b) is assumed, a relatively large ρ value should be observed. Furthermore, since in this

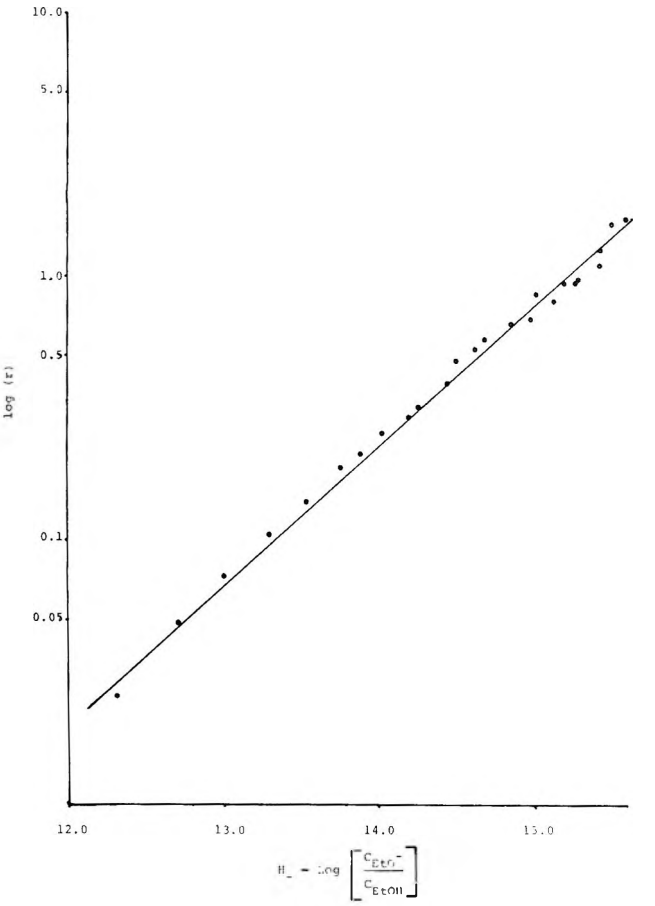


Figure 4. Logarithm of observed rate *vs.* H_- − log $[EtO^-]/[EtOH]$.

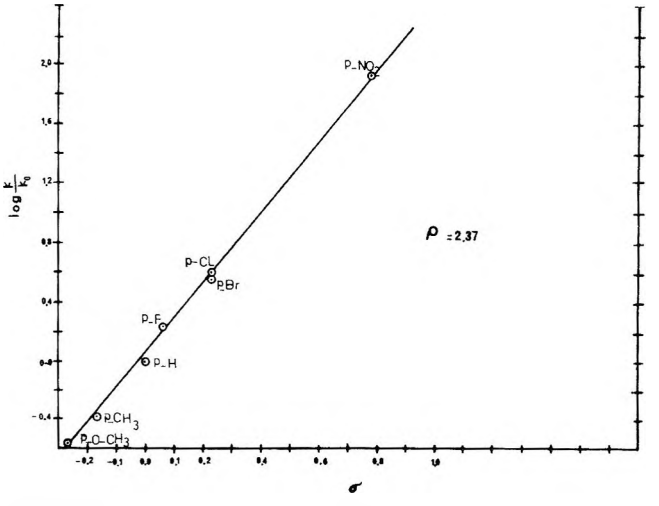
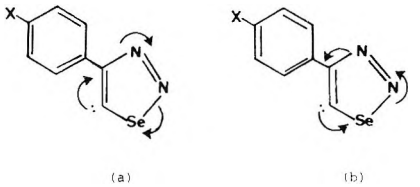


Figure 5. Hammet σ–ρ relation for the overall decomposition rate of AH at 32°.

case electron-withdrawing groups such as a *p*-nitro group would be in direct resonance with the reaction site, a σ^-

Scheme II



value would be a better substituent constant if transition state b were operative. As can be seen from Figure 5, the ordinary σ value of 0.78 gives a much better fit than a σ^- value of 1.27. It is therefore concluded that the mode of the unimolecular decomposition is probably according to (a) as previously assumed,[2] and that the substituents shift the equilibrium as discussed above.

Part II. Steps 3 through 5 of the reaction were studied by measuring the rate of appearance of the product PH starting with the intermediate C^- (see Scheme I). In all experiments only 50 to 75% of the expected product was obtained. Since no side reaction was identified under the conditions of the experiments, it was concluded that the starting material, Ph—C≡C—Se^-, was impure. The absence of a possible side reaction was checked kinetically by measuring the rate of appearance of PH *vs.* the rate of disappearance of C^- (see Figure 6). This figure also indicates the

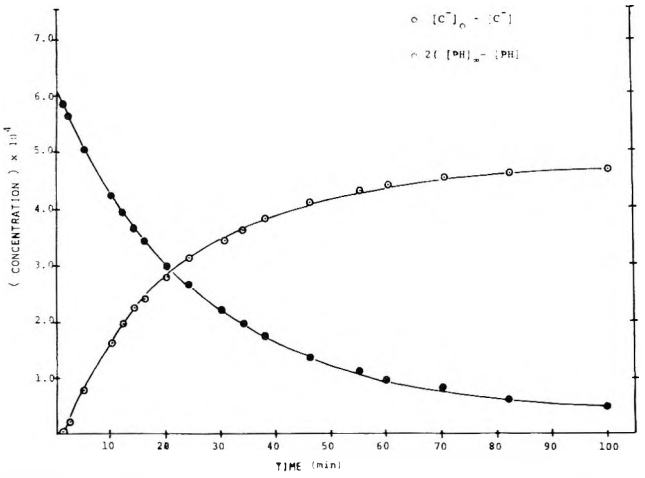


Figure 6. Disappearance of C^- and appearance of PH in 0.01 *M* EtO^-K^+ at 32°.

steady state condition of CH, and therefore implies that the selenaketene has a transient existence. The concentration of C^- was obtained by following the changes in maximum absorptions of C^- (at 308 nm) and PH (at 340 nm) as the reaction proceeded[6c] and solving two simultaneous equations for the respective concentrations.

Two different rate laws result depending on whether step 3 is general acid catalyzed (*i.e.*, $C^- + BH \rightleftharpoons CH + B^-$) or specific hydrogen ion catalyzed (*i.e.*, $C^- + BH_2^+ \rightleftharpoons CH + BH$). Denoting the rate constants for the forward and the reverse directions of step 3 by k_3 and k_{-3}, respectively, the differential rate laws obtained for the two cases are respectively

$$-\frac{d[C^-]}{dt} = 2\frac{d[PH]}{dt} = \frac{2k_3[BH][C^-]^2}{(k_{-3}/k_4)[B^-] + [C^-]} \quad (8)$$

$$-\frac{d[C^-]}{dt} = 2\frac{d[PH]}{dt} = \frac{2k_3[H^+][C^-]^2}{(k_{-3}/k_4)[BH] + [C^-]} \quad (9)$$

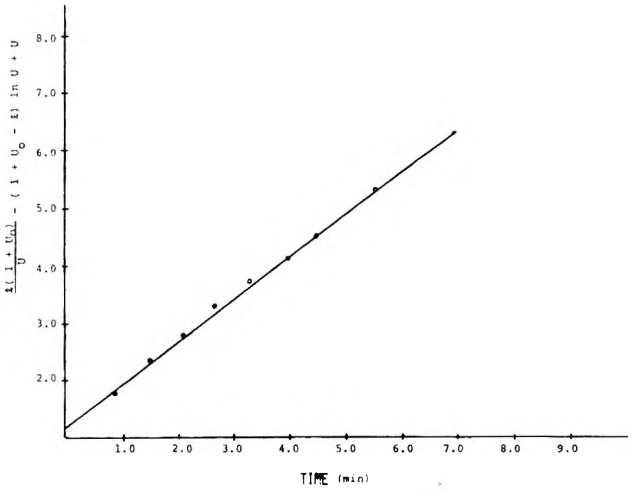


Figure 7. A plot of eq 11 with $[C^-]_0 = 1.3 \times 10^{-3}$ *M* and $[B^-]_0 = 1 \times 10^{-3}$ *M* *vs.* time in ethanol at 32°.

where steady state condition for CH and a rapid protonation of P^- are assumed. Preliminary analysis of the data showed that in general the two terms in the denominator of eq 8 and 9 are comparable in value and must both be retained. Hence the corresponding *initial* reaction rates

$$\frac{2k_3[BH][C^-]_0^2}{(k_{-3}/k_4)[B^-]_0 + [C^-]_0}$$

and

$$\frac{2k_3[H^+]_0[C^-]_0^2}{(k_{-3}/k_4)[BH] + [C^-]_0}$$

afford a ready distinction between eq 8 and 9 by means of their different dependencies on the initial base concentration $[B^-]_0$. Examination of the initial reaction rates obtained from the data showed an inverse proportionality to $[B^-]_0$ equivalent to a direct proportionality to $[H^+]_0$. Thus eq 9 and therefore specific hydrogen ion catalysis is clearly indicated.

To integrate eq 9, we use eq 7 to write

$$-\log [H^+] = \text{const} + \log [B^-] \quad (7')$$

Furthermore, from the stoichiometry of the reaction, the base concentration during the reaction is given by

$$[B^-] = [B^-]_0 + 2[PH]$$

The last two equations can be combined to give

$$\frac{[H^+]}{[H^+]_0} = \frac{[B^-]_0}{[B^-]} = \frac{[B^-]_0}{[B^-]_0 + 2[PH]} \quad (10)$$

which is inserted in eq 9, and the latter integrated to give

$$l(1 + U_0)\frac{1}{U} - (1 + U_0 - l)\ln U + U = 2qt + \text{const} \quad (11)$$

where

$$l = k_{-3}[BH]/k_4[B^-]_0$$

$$U = [C^-]/[B^-]_0$$

$$U_0 = [C^-]_0/[B^-]_0$$

$$q = k_3[H^+]_0$$

Figure 7 shows a typical plot corresponding to eq 11. The value of $k_{-3}BH]/k_4$ used was 3×10^{-4} *M*, which gave the best fit for the data. The maximum concentration of C^- taken was about 1×10^{-3} *M*. Therefore at base concentrations higher than about 0.01 *M*, the factors U_0 and l become negligible compared to unity, and eq 11 reduces to

Table I
Rate Constants of Step 3 in Ethanol at 32°

$[B^-]_0$, M	$2q$, min^{-1}	$2q[B^-]_0 \times 10^4$, $M\ min^{-1}$
1.1×10^{-3}	0.750	8.25
1.71×10^{-3}	0.366	6.3
3.26×10^{-3}	0.243	7.9
3.46×10^{-3}	0.233	8.2
3.83×10^{-3}	0.175	6.7
7.72×10^{-3}	0.083	6.4
8.90×10^{-3}	0.075	6.9
1.07×10^{-2}	0.064	6.8
1.22×10^{-2}	0.050	6.1
1.55×10^{-2}	0.044	6.8
1.94×10^{-2}	0.040	7.7

$$(1/U) - \ln U = 2qt + \text{const} \qquad (12)$$

The rate constants obtained using eq 11 and 12 are shown in Table I. The value of the product $2q[B^-]_0 = 2k_3[H^+]_0[B^-]_0$ nearly remains a constant in Table I, as it should for a given medium according to eq 7. It is somewhat surprising that this reaction displays a specific hydrogen ion catalysis in basic alcoholic media, where the concentration of H^+ is quite small.

Finally, the rates of phenyl-substituted Ph—C≡C—Se^- were compared and a ρ value of nearly zero was obtained. This is consistent with the interpretation that the small negative ρ value expected for step 3 is compensated by an equal and opposite ρ value for the dimerization of step 4.

When gas evolution was studied with 2-propanol as solvent, a different behavior in addition to the simple one encountered with ethanol was observed. The latter, *i.e.*, pseudo-first-order behavior described by eq 6, was observed when the initial base concentration was much greater than $[AH]_0$, so that its depletion during the reaction was negligible. However, contrary to the case of ethanol, at initial base concentrations comparable with or lower than $[AH]_0$, part II of the reaction did not occur rapidly enough to maintain a constant basicity. Thus the rate of gas evolution became dependent on the progress of part II of the reaction and *vice versa*. Therefore, contrary to the case of ethanol where parts I and II of the reaction were studied separately, 2-propanol afforded a simultaneous study of the two parts of the reaction *via* the rate of gas evolution. This difference of behavior between the two media is due to the higher inherent basicity of 2-propanol which causes a relative speed-up and slow-down of parts I and II, respectively. Although the above coupling is also possible in ethanol, the necessary conditions could not be realized with the volumetric capabilities used in the experiments.

A typical logarithmic plot of $(V_\infty - V_t)/V_\infty$ *vs.* t in 2-propanol displaying variable basicity is shown in Figure 8. This plot indicates that the basicity, which controls the rate of gas evolution, decreases from its initial value to a minimum (where it assumes a steady state) and then starts increasing to its initial value as the reaction proceeds to completion. Clearly parts I and II of the reaction are coupled *via* base concentration, and must be treated simultaneously. This is accomplished by combining the differential rate laws of the two parts [*cf.* eq 6 and 9], taking due account of the coupling.

$$-\frac{d[AH]}{dt} = \frac{d[N_2]}{dt} = k_2[A^-] = \frac{k_1k_2}{k_{-1}'}[B^-][AH] \qquad (13)$$

$$2\frac{d[PH]}{dt} = \frac{2k_3[H^+][C^-]^2}{(k_{-3}/k_4)[BH] + [C^-]} \qquad (9')$$

As before, $[H^+]$ is obtained by means of eq 7′ and the stoichiometric conditions

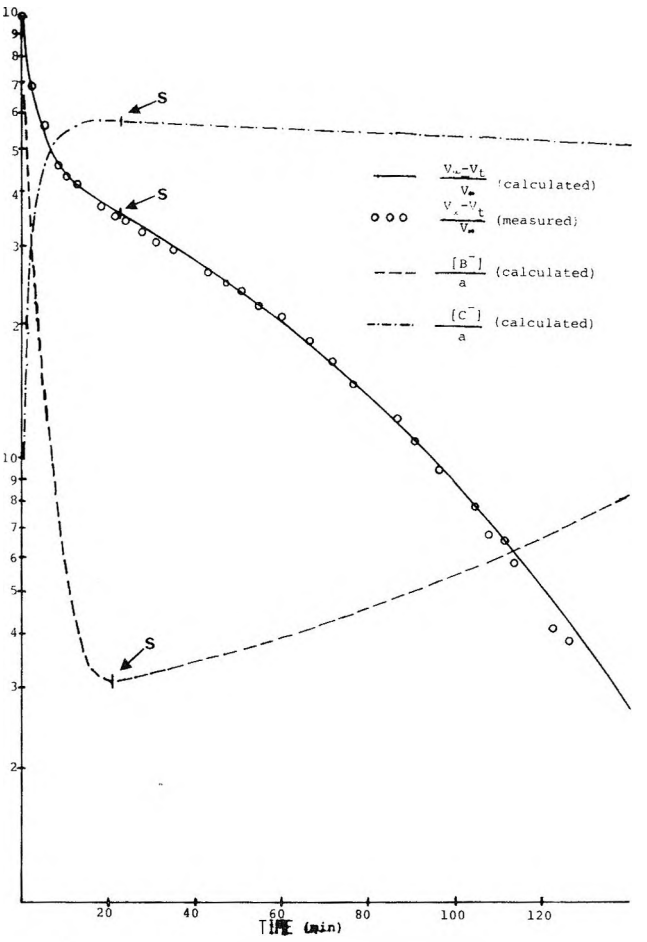


Figure 8. Overall reaction progress in dilute basic 2-propanolic solution at 32°.

$$\frac{[H^+]}{[H^+]_0} = \frac{[B^-]_0}{[B^-]} = \frac{[B^-]_0}{[B^-]_0 + 2[PH] - [N_2]} \qquad (14)$$

Denoting $[AH]_0$ and $[B^-]_0$ by a and b, and the amount of N_2 gas evolved and the concentration of C^- at time t by x and y, respectively, we obtain from eq 14

$$[H^+] = [H^+]_0\frac{b}{b - y} \qquad (15)$$

Equations 13 and 9′ then take the form of eq 16 and 17, respectively.

$$\frac{dx}{dt} = (k_1k_2/k_{-1}')(a - x)(b - y) \qquad (16)$$

$$\frac{d(x - y)}{dt} = \frac{2qby^2}{(b - y)(k_{-3}/k_4[BH] + y)} \qquad (17)$$

The differential eq 16 and 17 were integrated numerically on a CDC 6400 computer using Taylor's method.[12] The results of the computations for a typical experiment are shown in Figure 8, where the measured and calculated values for $(V_\infty - V_t)/V_\infty$ are compared, and the calculated values of $[B^-]/a$ and $[C^-]/a$ are also drawn in for reference.

In obtaining the calculated results displayed in Figure 8, the values $a = [AH]_0 = 7 \times 10^{-3}\ M$ (measured value) and $k_3[BH]/k_4 = 3 \times 10^{-4}\ M$ (obtained from the data of part II in ethanol) were used. The remaining parameters, *i.e.*, $b = [B^-]_0$, k_1k_2/k_{-1}', and q, were treated as free and were determined by a mean-square fit. The reason for treating b as a free parameter is the inaccuracy in its measurement at the concentrations used (*i.e.*, about $5 \times 10^{-3}\ M$). The reason for treating q as free is the unavoidable presence in small and variable concentrations of water in the alcohol used, which, because of the extreme sensitivity of the H_- value of 2-propanol to the addition of small amounts of

Table II
Parameters Obtained by Fitting Volumetric Data with 2-propanol as Solvent

Expt no.	$[B^-]_0 \times 10^3$, M	k_1k_2/k_{-1}' min^{-1} M^{-1}	$2q[B^-]_0 \times 10,^6$ M min^{-1}	$(2k_1k_2/k'_{-1}) \cdot q[B^-]_0 \times 10^4$, min^{-2}
1	5.5	79	1.8	1.4
2	6.1	69	2.0	1.4
3	4.9	67	1.6	1.0
4	4.4	61	2.1	1.3
5	4.7	41	3.2	1.3

water,[7] has a decisive effect on the value of this parameter. Table II shows the parameters obtained by fitting five representative experiments with apparently variable water content (experiment no. 2 is the one displayed in Figure 8). All fits were about equally good as judged from the mean-square deviation. Table II has been arranged in the order of decreasing values of k_1k_2/k_{-1}' and thus increasing water content. The value of $q = k_3[H^+]_0$ is thus expected to increase with increasing aqueous component. With the exception of experiment 3, this expectation is verified. Finally the product qk_1k_2/k_{-1}' should approximately remain constant, as the two factors are oppositely influenced by the increase of the aqueous component. Again, with the exception of experiment 3, this product is seen to be roughly constant. The above observations also serve to show that the fitting procedure s a fairly reliable one and yields meaningful results with very little input data.

We now proceed to give a qualitative interpretation of the results displayed in Figure 8. The initial decrease of basicity is accounted for by observing that, under these conditions, C^- accumulates to an appreciable concentration, thereby preventing the complete regeneration of the base consumed in step 1. Thus concurrent with the accumulation of C^- as the reaction proceeds, $[B^-]$ decreases, and consequently part I of the reaction is hindered while part II is enhanced. The changes just mentioned continue until the two parts of the reaction equilibrate, at which time $[B^-]$ and $[C^-]$ reach their minimum and maximum values, respectively. This stage corresponds to the points S of Figure 8, where the rate of gas evolution is clearly at its minimum. The "steady state" just described will subsequently be disturbed as the depletion of B^- causes a corresponding decrease in the rate of the production of C^-, thereby forcing the latter to decrease and $[B^-]$ to increase. Thus the last stage of the reaction is characterized by increasing basicity and rate of gas evolution. Finally at the completion of the reaction, [AH] and $[C^-]$ go to zero while $[B^-]$ returns to its initial value. Note that Figure 8 does not continue to completion, since the rate of gas evolution becomes unmeasureably small long before the accumulated C^- converts into the final product. As is evident from Figure 8, the complete conversion of C^- will take several hours.

Acknowledgment. We wish to thank Mr. S. G. Shirazi for his assistance in the preliminary stages of this work, Mr. A. A. Mohseni for his programming of the computations, and the Bioengineering Center of Arya-Mehr University for the use of their respirometer.

Supplementary Material Available. Plots of gas evolution *vs.* time, observed rate *vs.* $[B^-]_0$ and changes in absorbance maxima of C^- and PH will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3906.

Registry No.—ω-d_3-Acetophenone, 17537-31-4; phenylacetylene, 536-74-3; deuterium oxide, 7789-20-0; 4-phenyl-5-*d*-1,2,3-selenadiazole, 53060-19-8; potassium phenylethynylselenolate, 36928-61-7; 4-phenyl-5*H*-1,2,3-selenadiazole, 25660-64-4; 1-deuterioethanol, 1624-36-8.

References and Notes

(1) (a) Department of Chemistry; (b) Department of Physics.
(2) I. Lalezari, A. Shafiee, and M. Yalpani, *J. Org. Chem.*, **38**, 338 (1973).
(3) J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and C. Sheppard, *Advan. Heterocycl. Chem.*, in press.
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(6) Figures a, b, and c will appear following this article in the microfilm edition of this journal. See paragraph at end of paper regarding supplementary material.
(7) (a) At higher base concentrations than about 0.7 *M*, the reaction is too rapid to be measured in ethanol. Actually, the excessive heat of solution of the base at about 1 *M* concentration disturbs the thermal equilibrium of the medium and thus prohibits measurements in the otherwise suitable medium methanol. (b) K. Bowden, *Chem. Rev.*, **66**, 119 (1966).
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(9) J. F. Bunnett and F. D. Olsen, *Can. J. Chem.*, **44**, 1899, 1917 (1966).
(10) The *m/e* 102 rather than the molecular ion was chosen for the measurement, since (a) it was the base peak in the spectrum and (b) it contained no selenium. The latter, because of its multiple natural abundance peaks, would have complicated ratio measurements.
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(12) The accuracy of the computation was controlled and set to be uniformly better than three significant figures.

Potassium Hydride, a Highly Active New Hydride Reagent. Reactivity, Applications, and Techniques in Organic and Organometallic Reactions[1-3]

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Potassium hydride is extremely reactive both as a base and as a hydriding agent. In both of these reactions it is far more reactive than either sodium hydride or lithium hydride. Potassium hydride surpasses finely divided potassium metal as a base yet possesses none of the latter's electron-transfer properties (reduction, coupling, etc.). KH reacts rapidly at 20–25° with excess triethylmethanol to yield the alkoxide quantitatively in <1 min, in contrast to K (80% complete in 20 min with very slow further reaction), NaH (5% in 20 min), and LiH (0% in 20 min). KH also rapidly metalates unhindered amines (*e.g.*, pyrrolidine) and dimethyl sulfoxide. In tetrahydrofuran suspension, metalation similarly proceeds rapidly with highly hindered weak acids such as bis(trimethylsilyl)amine (pK_A = 28–29), *N*-isopropylaniline (pK_A = 26), triethylmethanol (pK_A = 22), and 2,6-di-*tert*-butylphenol (pK_A = 17–18). Under comparable conditions, only the latter reacted significantly with NaH; none react with LiH. Ketones are metalated to potassium enolates in high to quantitative yield; no reduction of carbonyl groups by hydride is observed. KH reacts rapidly with weak and hindered Lewis acids under conditions where NaH is very sluggish and LiH is essentially inert. Hindered trialkylboranes are readily converted to the corresponding borohydrides ($K^+ {}^-HBR_3$) at room temperature; the very weakly acidic triisopropyl borate reacts similarly. Reactions with KH appear to be entirely heterogeneous, occurring at the crystal surface. Potassium hydride is thermally stable and readily handled as a dispersion in mineral oil. In the absence of the protective oil, it must be protected from air and moisture. Detailed handling procedures are discussed.

Saline hydrides are potentially attractive as strong bases, metalating agents, and hydride sources:[4a] they are insoluble in nonreactive organic solvents[5] and readily separated from products; the acid–base reaction is essentially irreversible; the sole by-product of metalation is an inert insoluble gas (H_2) and there is none at all from hydride transfer; the equivalent weights are lower than those of the analogous amides, alkoxides, etc.; the hydrides are prepared directly from the elements[6] and are indefinitely stable; and the three lower members of the series are commerically available. The chief drawback arises from the insolubility: reactions apparently proceed at the crystal surface with the usual problems of such reactions (surface area effects, poisoning, etc.).

Of the saline hydrides, only NaH has found extensive use in synthesis.[7-10] In general, NaH has been successful only in reactions involving relatively acidic compounds (*e.g.*, ethyl acetoacetate, unhindered alcohols); metalation of rather less acidic compounds (*e.g.*, cyclohexanone, indene) requires prolonged heating.

Examination of the physical and thermochemical properties of the group I hydrides suggests that reactivity should increase proceeding down the group to CsH. The crystal lattice energies[4b,11] decrease considerably from LiH to CsH, and the "apparent" hydride ion radius[4c] in the crystal increases from LiH to KH and then is nearly constant (Figure 1). As reactions of the hydrides apparently proceed at the crystal surface, the lower lattice energy would be expected to be reflected in a greater facility of reaction, which involves removal of M^+ and H^- from the crystal. The larger hydride radius could reflect lower covalency or less compression of H^-; either would be expected to increase reactivity. KH appeared to present the optimum balance of potential reactivity and practical considerations (availability, cost, etc.). In fact, KH has proven remarkably reactive, markedly more so than NaH.

Results and Discussion

Reactivity. Reactivity of the hydrides and of potassium metal was initially compared in reactions with an excess of pyrrolidine, dimethyl sulfoxide, and triethylmethanol. Pyrrolidine is completely metalated in 2–3 hr at room temperature by KH, while no reaction is observed with either a potassium dispersion or NaH. At elevated temperatures (≥75°), both K and NaH react slowly liberating hydrogen; however, at 75° the amide evidently undergoes secondary decompositions as fast as formed for the solutions never develop sufficient base strength to deprotonate triphenylmethane indicator detectably. KH reacts rapidly (8 min) with dimethyl sulfoxide at 25°, whereas NaH requires a temperature of 70–75° for reaction.[12,13] Triethylmethanol reacts completely with KH in less than 1 min at 25°, while NaH reacts only slightly in 0.5 hr. With K, the reaction is moderately rapid initially but becomes very sluggish after 60–75% reaction. In all three cases, LiH failed to react under comparable conditions at 25° (Figure 2).

Solvents. The solvents which appear most suitable for reactions of KH are ethers, especially tetrahydrofuran (THF) and the glyme solvents. Aliphatic and aromatic hydrocarbons are inert to KH—no metalation of alkylbenzenes such as toluene occurs even at 100°—but many reactions are more sluggish in these solvents, possibly due to coating of the KH surface by the insoluble products. Ketones, esters, and nitriles with α hydrogens react rapidly with condensation. Primary and secondary amides, anilines, and alcohols are rapidly metalated. Dimethylformamide appears to be reduced, yielding dimethylamine upon hydrolysis; this is so far the only observed reduction of a carbonyl group at 25° by KH. Dimethyl sulfoxide is rapidly metalated. Hexamethylphosphoric triamide and tetramethylurea appear stable at room temperature, but some loss of KH activity occurs in suspensions maintained at elevated temperatures (≥75°). Prolonged stirring of KH with nonreacting solvents (*e.g.*, THF), followed by decantation, reveals no detectable dissolved hydride.

Many of the potassium salts produced by metalation with KH are moderately to highly soluble in THF, as are the complex borohydrides from hydriding of alkyl and alkoxyboranes; in cases of low solubility, addition of 1–2 equiv of triglyme may markedly improve solubility, presumably by increased solvation of K^+. Potassium alkoxides and potassium trialkylborohydrides are generally soluble in hydrocarbons.

Tetrahydrofuran appears to be the medium of preference for metalation and hydriding reactions and has been generally employed in the reactions discussed below.

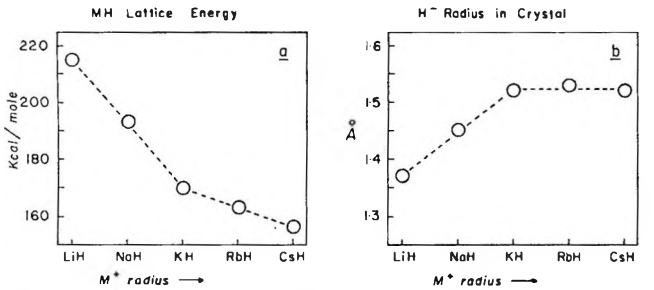


Figure 1. Group I saline hydrides: (a) crystal lattice energy (*cf.* ref 4b and 11); (b) effective hydride ion radii in crystal from lattice constants and Goldschmidt radii of metal ions (*cf.* ref 4c).

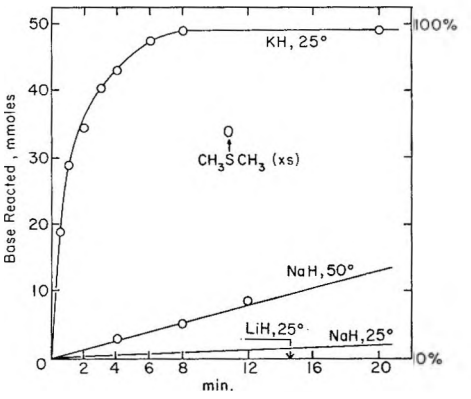
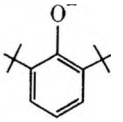


Figure 2. Reaction of group I saline hydrides with excess dimethyl sulfoxide (DMSO) as solvent to yield methylsulfinylmethide ("dimsyl") ion. Comparable figures of reactivity of the hydrides and potassium metal with amines and alcohols have been published (*cf.* ref 3b).

Metalation of O–H and N–H. A wide variety of weakly acidic O–H and N–H-containing compounds react rapidly with KH in THF suspension to yield the corresponding potassium salts quantitatively. Among these are carboxylic acids, phenols, alcohols, primary and secondary amides, and anilines. Aliphatic amines are generally unreactive in THF, but ethylenediamine in excess (2:1 EDA–KH) is metalated in 1–2 hr to yield a suspension of the alkamide; the alkamide suspension is relatively unstable, losing base activity (by titration using triphenylmethane as an indicator[14]) through attack on solvent.

Of particular interest is the facile preparation of such synthetically useful hindered bases as bis(trimethylsilyl)amide (I),[15] *N*-isopropylanilide, trialkylmethoxide (II),[16] and 2,6-di-*tert*-butylphenoxide (III).[17] In these cases reaction with potassium metal is sluggish or nonexistent, and—as expected—NaH and LiH are generally unreactive. The procedure is simple and direct: addition of the conjugate acid to a suspension of KH in THF; controlled addition is necessary in most cases to prevent excessively vigorous hydrogen evolution. Metalations are generally carried out with a slight excess of hydride which may be removed by filtration or decantation (the phenoxide is slightly soluble in the absence of polyether cosolvents); use of an excess of the acid or stoichiometric quantities is also satisfactory, although for obvious reasons longer reactions times result. Glyme solvents are equally satisfactory; benzene or cyclohexane function well only in the case of alkoxides. Reaction times with 1.25 equiv of KH vary from 1 min (2,6-di-*tert*-butylphenol) to 30 min (bis(trimethylsilyl)amine). Metalations of these sterically hindered compounds have been tabulated in ref 3e.

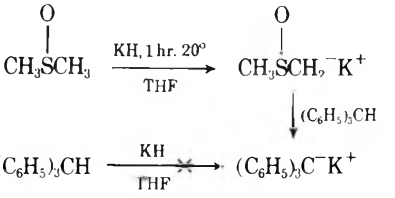
$(CH_3)_3SiNSi(CH_3)_3$ R_3CO^- 

I II III

R = C_2H_5, C_6H_{11}, etc.

Metalation of C–H. Potassium hydride in THF rapidly metalates a variety of weak carbon acids such as cyclopentadiene (pK_A[18] = 15), fluorene (pK_A[18] = 23–25), and dimethyl sulfoxide (DMSO) (pK_A[18] = 31–35); in contrast, NaH reacts readily only with the most acidic compounds (*e.g.*, cyclopentadiene). Triphenylmethane is not directly metalated by KH in THF at an appreciable rate but may be metalated through *in situ* formation of "dimsyl" potassium ($CH_3SOCH_2^-K^+$); the use of catalytic quantities of DMSO appears feasible but has not been generally explored (Scheme I).

Scheme I



Ketones (pK_A[19] ≈ 21)—as well as the more acidic β-dicarbonyl compounds—react very readily with KH in THF to yield the potassium enolates, in most cases quantitatively. Hindered ketones such as 2,4-dimethyl-3-pentanone, 2,6-dimethylcyclohexanone, and isobutyrophenone are completely metalated in 10–15 min at room temperature.

Reaction of ketones with LiH and NaH has been observed to be very sluggish. Relative reactivity of the hydrides has been compared for metalation of pinacolone in THF at 20°, pinacolone presenting a readily available structure relatively open to reaction with base yet hindered toward aldol condensation and reduction. The contrast between the various metal hydrides is striking; complete 20% and 5% reaction, respectively, in 2 hr.[20a]

To confirm that these results were not artifacts of particle size differences, a particularly finely divided dispersion of NaH was obtained.[21] Examination with a calibrated field microscope showed a range of particle sizes, with the most prevalent being a needle of ~3-μm diameter; KH appears as cubes with the most common size being 6–8 μm in diameter. Sedimentation in pentane (NaH has only a slightly lower density than KH) was much slower with this NaH sample than with KH, indicating a considerably higher proportion of fines. Despite the apparently greater degree of dispersion of this NaH sample, it was *still* markedly less reactive than KH toward pinacolone, 60% reaction in 2 hr (*vs.* 100% in 5 min for KH). We believe this confirms that greater reactivity is inherent in KH.

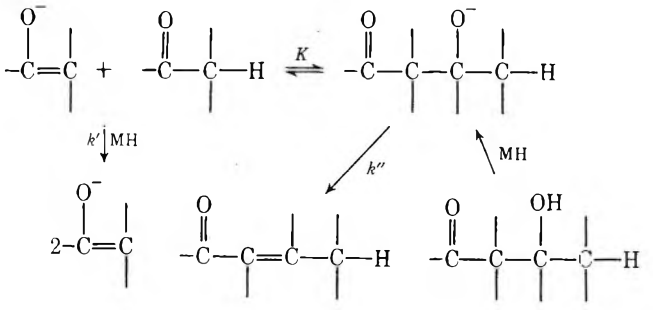
Many ketones—especially unhindered cyclic or methyl ketones—suffer substantial aldol condensation in competition with metalation by lighter saline hydrides.[20b] However, with KH condensable ketones such as 2-heptanone, cyclohexanone, acetone, and even cyclopentanone are metalated in 80–100% yield. The lack of competing aldol condensation may reflect the speed of KH metalation, removing ketone from the aldol equilibrium (Scheme II) faster than irreversible enone formation occurs. Moreover, the aldol equilibrium appears to be favored by tightly associating cations[22a] and Na^+ appears more associated than K^+. Thus K in Scheme II is smaller for potassium than for sodium, while k' is obviously much larger, producing the observed efficiency of KH for metalating ketones. In fact, if the aldol product 4-hydroxy-4-methyl-2-pentanone is

Table I
Kaliation of Ketones at 20°

Compd[a]	Registry no.	Time, min	Enolate yield,[b] %	% *less* substituted enolate[c]
		Methyl Ketones		
Acetone	67-64-1	1.5	90	
2-Heptanone	110-43-0	1.5	100	46
3-Methyl-2-butanone	563-80-4	1	101	88
		30 (−78°)[d]	98	>99
3,3-Dimethyl-2-butanone	75-97-8	5	97	
Cyclopropyl methyl ketone	765-49-5	1	100	100
		Methine Ketones		
Isobutyrophenone	611-70-1	12	97	
2,4-Dimethyl-3-pentanone	565-80-0	10	100	
		Cyclic Ketones		
Cyclopentanone	120-92-3	2	81	
Cyclohexanone	108-94-1	1.5	90	
2-Methylcyclohexanone	583-60-8	6	96	33
		30 (−78°)[d]	98	95
		α,β-Unsaturated Ketones		
Mesityl oxide	141-79-7	1	97	*e*
Carvone	99-49-0	20	35	*e*
Pulegone	89-82-7	7	98	*e*

[a] 25.0 mmol of ketone, 28–35 mmol of KH, 40–50 ml of THF solution. [b] Ketone recovered after quenching with water and acid, glpc. [c] Isomers trapped with trimethylchlorosilane and triethylamine. [d] Metalation with potassium bis(trimethylsilyl)-amide (I) formed *in situ*. [e] Products appeared to be entirely the conjugated dienolate.

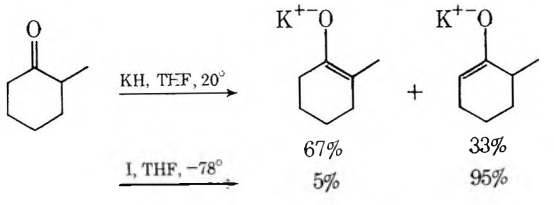
Scheme II



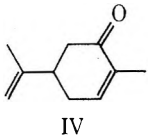
treated with KH, 2.0 equiv of hydrogen is evolved and acetone enolate is formed quantitatively; no mesityl oxide is observed.

Metalation with KH yields an equilibrium mixture of the potassium enolates directly. Sterically (kinetically?) controlled metalation may be achieved by first metalating bis(trimethylsilyl)amine (*vide supra*) *in situ* and thence adding the ketone at low temperature (Scheme III).

Scheme III



Metalation of α,β-unsaturated ketones proceeded smoothly with β,β-dialkyl structures yielding, as expected, the dienolate anion. Systems less hindered toward Michael addition such as carvone (IV) undergo substantial polymerization; methyl vinyl ketone and ethyl vinyl ketone were completely polymerized.

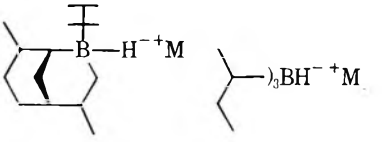


IV

In no case was reduction observed to compete with metalation by KH.

Kaliations of ketones are summarized in Table I.

Hydride Transfer to Weak Lewis Acids. Considerable interest has been generated recently in complex borohydrides as reducing agents.[23] Certain of these have been prepared directly by reaction of organoboranes with LiH.[23c,24] However, increases in hindrance or decreases in Lewis acidity of the boron compounds and changes from ethers to hydrocarbon solvents inhibit or prevent reaction.[24a] The hindered trialkylborohydrides V and VI (M = Li)—highly stereoselective reducing agents—have been prepared only by indirect means.[23d,e]



V VI

BX_3

VIIa, X = *sec*-Bu
b, X = O—*i*-Pr

Potassium hydride reacts rapidly with even very hindered and weakly acidic boron compounds in THF, providing the only direct, general method for quaternizing boron with hydride. Much of this activity is retained in hydrocarbon solvents as well. These results are summarized in Table II.

In contrast to the facile reactions of KH, NaH and LiH were sluggish or unreactive.[25] With VIIa, NaH reacted only 10% in 8 hr and LiH is inert.[26] With VIIb, both NaH and LiH are unreactive in THF at 25°, though reaction of NaH has been reported at high temperatures.[27]

Poisoning of KH. No systematic survey of poisoning agents has been made. Experience shows, however, that KH which has been exposed to atmospheric moisture tends to be less reactive and show induction periods in its reactions, possibly because of surface coating by KOH. Such samples can often be activated by stirring with a small amount of methyl iodide in THF. Trimethylchlorosilane is

Table II
KH Hydride Transfer to Boron Lewis Acids (BX_3)[a]

X	Registry no.	Solvent[b]	Temp, °C	Time, min	B-H yield, %
Et	97-94-9	THF	5–10	15[c]	100
Et		$PhCH_3$	20	30[c]	97
n-Bu	122-56-5	THF	20	60	101
i-Bu	1116-39-8	THF	20	60	96
i-Bu		$PhCH_3$	20	750	81
sec-Bu	1113-78-6	THF	20	60	100
i-PrO	5419-55-6	THF	20	60	100

[a] 25 mmol of BX_3 with 35–50 mmol of KH dispersed in the indicated solvent. [b] Concentration of BX_3 = 0.95–1.0 *M*; 0.65–0.70 *M* for $(i\text{-}PrO_3)_3B$. [c] BEt_3 added dropwise over 5 min with cooling.

a very effective poison and attempts to effect metalations in its presence (*e.g.*, to achieve trapping of kinetically generated anions) have uniformly proven unsuccessful. Similar results have been reported with NaH;[28a] in this case it was suggested that traces of alkoxide acted as a "carrier" in metalations, these being removed by the silylating agent. We feel this is unlikely as the poisoning effect remains even if the silylating mixture is replaced by fresh solvent. Possibly the poisoning represents a reduction of the Si–Cl bond, with the surface of the KH crystal being converted to KCl or a potassium silyl.[28b,c]

Handling of KH. Because of the much higher reactivity of KH compared to that of the widely used NaH, the rather cavalier treatment often accorded the latter is both unsuitable and hazardous. With reasonable precautions KH may be handled with both safety and ease; our experience is fully described in the Experimental Section.

Experimental Section

Storage and Transfer of KH. Potassium hydride has been obtained currently[29] as a dispersion in mineral oil containing 20–35% KH by weight.[30] Although pure KH is a white powder, most samples obtained were gray, presumably due to traces of unreacted potassium.[31] Potassium hydride reacts slowly with oxygen. We have stored it (a) in glass bottles or (b) in polyethylene bottles kept in inert atmosphere or sealed with varnish to prevent diffusion of oxygen.

Upon standing, KH segregates from the oil and with prolonged storage the material becomes compacted, requiring rather vigorous attack to achieve initial dispersion.[32]

Transfers of KH in oil may be made quickly in air without difficulty but for prolonged handling (*e.g.*, initial dispersing of the compacted mass) a glove bag (N_2 or Ar) is desirable. Routine transfers are performed directly from the storage container. Two holes just sufficient to accept 18–19 gauge hypodermic needles are punched in the polyethylene container near the screw cap. Through one hole a vigorous stream of dry nitrogen is introduced with a short needle, providing a backflush during transfer. The dispersion is transferred using a medicine dropper having a 2–3-mm orifice.[33] The container is then capped and purged with nitrogen, and the cap and holes are sealed with tape, paraffin, etc.

Utensils and glassware coated with KH–oil may be cleaned by rinsing with a 10% solution of an alcohol in hydrocarbon (*e.g.*, kerosene).

Caution! Under no conditions should KH–oil be directly placed in water or ignition may occur. Disposal of organic solvents containing even traces of KH in sinks will produce a fire.

Standardization of KH. A weighed sample of the KH dispersion (1–2 g) is placed in a flask equipped with a TFE-covered magnetic stirring bar, condenser, and injection port capped with a rubber sleeve stopper. The apparatus is purged with nitrogen and connected through traps to a gas-measuring device. The flask is immersed in a water bath and, with stirring, 20 ml of 2-butanol is added, dropwise at first until hydrogen evolution moderates. The KH present is determined by a standard gas law calculation of the hydrogen liberated (1.0 H_2 = 1.0 KH).

The resulting solution in the flask may be diluted with water and titrated to a phenolphthalein end point. Substantial excesses (>5%) of total base over hydride base (from gas evolution) indicate significant hydrolysis of the original KH sample.

Separation of KH from the Oil Matrix. The KH is placed in the apparatus described above, with a mercury bubbler replacing the gas-measuring device. Dry pentane, ether, or similar solvent[34] is added: 5–10 ml/g of dispersion. The mixture is stirred briefly and allowed to settle with occasional tapping, and the solvent–oil solution is removed with the syringe. Three such washings remove all but traces (<1%) of the oil. To facilitate removal of the solvent, an 18–20 gauge flat-tipped needle 8–10 in. long is used.[35] The solvent washed may contain traces of highly reactive KH fines and *must* be treated with a lower alcohol before disposal. Fine KH particles almost inevitably cause ignition if spent washes are disposed of in sinks, etc.

Residual solvent is removed under vacuum or with a stream of N_2 or Ar.

Potassium Pyrrolidide. In the apparatus described above was placed 25 mmol, 1.0 g dry basis, of KH; the oil was removed with pentane. To the dry KH was added 25 ml of pyrrolidine (distilled and dried over 4A molecular sieve). Reaction at 25° proceeded smoothly at a moderate rate, with hydrogen evolution ceasing at 95% of the theoretical amount (based on KH) in 2 hr. Yield of amide was 93% (based on KH, 98% based on H_2 evolved) by titration with 2,6-di-*tert*-butylphenol in benzene using triphenylmethane as an indicator (blood red → colorless). The alkamide was apparently largely insoluble in the pyrrolidine, the reaction mixture being a grayish slurry; addition of up to 75 ml of pyrrolidine did not appear to allow dissolution of the majority of the solid.

Addition of 20 mmol of bromobenzene to a suspension of potassium pyrrolodide "1 *M*" at 25–30°, followed by quenching with water, yielded after distillation 90% (based on bromobenzene) of *N*-phenylpyrrolidine.

Potassium Methylsulfinylmethide ("Dimsyl"). In the apparatus described above (125 ml flask) was placed 25 mmol, 1.0 g dry basis, of KH freed of oil with pentane as described above. The flask was cooled in a 10° water bath and 25 ml of dimethyl sulfoxide (dried over 4A molecular sieve) was added with stirring. Vigorous hydrogen evolution began immediately and was quantitative in minutes. The resulting solution was nearly clear and straw colored; the yield was 96% by titration with 2,6-di-*tert*-butylphenol in benzene.

Potassium Bis(trimethylsilyl)amide. Excess Metalating Agent. In the apparatus described above (125-ml flask) was placed 31.2 mmol, 1.25 g dry basis, of KH. After removal of oil, 20 ml of THF (dried over 4A molecular sieve) was added, followed by 25 mmol, 5.2 ml, of distilled bis(trimethylsilyl)amine with cooling (20°) and vigorous stirring. Hydrogen evolution was quantitative in 15 min.[36] After standing unstirred for 30 min, the slightly turbid base solution could be decanted from excess KH; several hours was required for complete settling of suspended matter.

Excess Substrate. The previous procedure was carried out using 25 mmol of KH and 35 mmol of bis(trimethylsilyl)amine. The resulting slightly turbid solution could be clarified by settling or anaerobic filtration through a thin pad of diatom filter aid; however, the turbidity has not affected any preparative uses of the amide solution.

In a similar manner, alkoxides and phenoxides were formed; 2,6-di-*tert*-butylphenol, a solid, was added slowly (vigorous hydrogen evolution) as a concentrated THF solution.

Potassium Enolate of 2,4-Dimethyl-3-pentanone. The ketone, 25 mmol/ml, was added to a suspension of 30 mmol, 1.2 g, of KH in 95 ml of THF at 20° with vigorous stirring. Hydrogen evolution was quantitative in 12–15 min; enolate yield was quantitative (by glpc after quenching with dilute HCl and addition of standard). A centrifuged sample of the enolate solution was free of ketone carbonyl by ir (1718 cm^{-1}) and showed an absorption for the enolate ion at 1604 cm^{-1}.

Potassium Enolate of 2-Methylcyclohexanone. Sterically–Kinetically Controlled Enolate Formation. Potassium bis(trimethylsilyl)amide was generated as described above (excess substrate procedure) from 27.5 mmol of KH and 30 mmol of distilled bis(trimethylsilyl)amine. The resulting solution, used directly without filtration, was cooled to −78° and 10 ml of a 2.5 *M* solution of 2-methylcyclohexanone in THF was added dropwise over 30 min with vigorous stirring. The yield of enolate was 95% (by glpc after quenching with dilute HCl and addition of standard); reaction of a sample of enolate solution with excess triethylamine–trimethylchlorosilane to trap the enolate[28a] revealed the enolate to be predominantly (95%) the *less* substituted isomer. Direct reac-

tion of 2-methylcyclohexanone with KH at 20° yielded a 2:1 mixture containing chiefly the *more* substituted enolate isomer, the equilibrium mixture at 20–25°.[37]

Potassium Tri-*sec*-butylborohydride. In the apparatus described above (125-ml flask) was placed 35 mmol, 1.40 g dry basis, of KH, and the oil was removed with pentane. The KH was suspended in 20 ml of THF and 25 mmol, 6.0 ml, of pure tri-*sec*-butylboron was added in one portion with stirring. After 1 hr at 20° in a water bath, reaction was quantitative (by hydrolysis of a centrifuged sample). The product has a 1:1:1 ratio of K^+ (as total base) to H^- (as hydrogen after hydrolysis) to boron (as 2-butanol after oxidation with $NaOH-H_2O_2$[38]). The solution separated from excess KH exhibited a broad ir absorption at 2025 cm^{-1} (B–H str) absent in solutions of tri-*sec*-butylboron.

Similar results were obtained by adding a THF solution of 25 mmol of tri-*sec*-butylboron—prepared *in situ* by hydroboration[38] of excess 2-butene—to dry KH. The yield was 93%.

Either of the above solutions rapidly reduced cyclic ketones at 0° to −78° to yield alcohols of the *less* stable stereochemistry. Thus 2-methylcyclohexanone and 4-methylcyclohexanone yielded at 0° the corresponding alcohols quantitatively with >99% and 88% cis stereochemistry, respectively.

Potassium Triethylborohydride. To KH, 30 mmol, suspended in THF or toluene (*vide supra*) was added *dropwise*, with ice cooling, 25 mmol, 3.5 ml, of triethylboron (Ethyl Corp.; *caution!* spontaneously flammable in air) over 2–3 min with vigorous stirring. The mixture was allowed to warm to 20° over 30 min; the yield is quantitative. The ir spectrum of the THF solution separated from excess KH showed a broad absorption at 1975 cm^{-1} [39] with shoulders at 2010 and 2070 cm^{-1} (B–H str), absent in triethylboron.

The THF solution of potassium triethylborohydride rapidly reduced alkyl halides in the manner reported[23c] for the lithium analog.

Potassium Triisopropoxyborohydride. In the apparatus described above was placed 50 mmol, 2.0 g dry basis, of KH, and the oil was then removed with pentane. The KH was suspended in 30 ml of THF and 25 mmol, 5.8 ml, of freshly distilled triisopropyl broate[40] was added. After stirring for 30 min at 20–25°, the yield of the borohydride was quantitative; a centrifuged solution contained a 1:1:1 ratio of K^+ (as total strong base) to B (by titration[27] in the presence of mannitol) to H^- (as hydrogen liberated by hydrolysis with aqueous HCl).

The solution of potassium triisopropoxyborohydride reduced 2-methylcyclohexanone stereoselectively to the cis alcohol (95.5%) at −23°; even at 0° reduction of esters and alkyl halides was observed to be very slow or nonexistent.

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Registry No.—KH, 7693-26-7.

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(30) Dispersions with greater than 40% by weight are too viscous for convenient handling.
(31) Reactivity and assay (±3%) appear unrelated to the degree of color; even dark grayish brown samples have been highly reactive, although the reaction product may be colored.
(32) A long-bladed screwdriver has proven the most efficient, if inelegant, tool for this purpose. Once dispersed, aggitation once or twice a month prevents hard compaction. A polyethylene- or TFE-covered magnet left in the container has proven excellent for achieving smooth dispersions.
(33) Syringes prove unsatisfactory due to "jamming" of the plunger by the KH powder.
(34) (a) Solvents obviously should be dry and free of protic materials. Moder-

ate amounts of unsaturated hydrocarbons appears to have no effect. (b) It is desirable that solvents have a low viscosity and density to facilitate settling of the KH particles. KH has a crystal density of 1.43 g cm^{-3}.

(35) (a) Available from the Hamilton Co., Whittier, Calif. (b) When using a flat-tipped needle, it is necessary to puncture the rubber-sleeve stopper with a regular needle first.

(36) Occasionally short induction periods have been observed especially with samples of KH that have been exposed to the atmosphere repeatedly. In such cases slower metalation (1 hr) has occurred.

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Kinetics and Mechanism for Hydrolysis of Substituted α,α-Dichlorotoluenes

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The rate of hydrolysis of α,α-dichlorotoluene and the corresponding *p*-chloro- and *p*-methyl derivatives in aqueous solution is independent of pH over the range 2–11. The reactivity of these substrates is very sensitive to the nature of polar substituents: the relative rates of hydrolysis of the *p*-chloro, unsubstituted, and *p*-methyl compounds is 0.6:1:78. Hydrolysis of these substrates exhibits values of entropy of activation in the range −8 to −13 eu. Salt effects on the rate of hydrolysis of α,α-dichlorotoluenes are small but hydrolysis is markedly retarded by addition of dioxane. Rate constants measured in 50% aqueous dioxane are 600–1000 times as small as those measured for the same substrates in water. Hydrolysis of these substrates is also subject to inhibition by both cationic and anionic surfactants: diminutions in rate between 10- and 100-fold are observed in the presence of 0.05 *M* surfactants. These data corroborate a mechanism of hydrolysis involving rate-determining unimolecular carbon–chlorine bond cleavage.

Mechanism and catalysis for hydrolysis of acetals and ketals[1-3] and related species[4,5] have been vigorously studied. As a consequence, a substantial body of experimental information is available on which to base conclusions concerning mechanism and to found predictions concerning the behavior of novel compounds in the same class. In contrast, rather little study of the hydrolysis of α,α-dichlorotoluenes has been undertaken, although there is substantial reason to believe that these reactions occur with rate-determining unimolecular cleavage of a carbon–chlorine bond.[6-8] However, little information is available concerning structure–reactivity relations, solvent effects, salt effects, and effects of ionic surfactants for these reactions. We report here results of an investigation of the kinetics of hydrolysis of substituted α,α-dichlorotoluenes in aqueous solution and other media designed to provide such information.

Experimental Section

Materials. α,α-Dichlorotoluene, *p*-methyl-α,α-dichlorotoluene, and *p*, α, α-trichlorotoluene were synthesized from the appropriate benzaldehydes and phosphorus pentachloride as previously described.[9] Ir and pmr spectra revealed no detectable impurities in these preparations. 1,4-Dioxane was obtained from the Eastman-Kodak Co. and was purified by distillation and passage through a column of neutral aluminum oxide (M. Woelm). Sodium dodecyl sulfate was obtained from the British Drug Houses Ltd., and was purified as previously described.[10] Dodecyltrimethylammonium bromide and hexadecyltrimethylammonium bromide were purified samples donated by the Department of Chemistry, Indiana University. All other reagents were of the best grade commercially available. Distilled water was employed throughout.

Kinetic Measurements. Hydrolysis of substituted α,α-dichlorotoluenes was followed spectrophotometrically by monitoring the appearance of the appropriate benzaldehyde as a function of time. Substrate concentrations near 10^{-4} *M* were employed. All measurements were made with a Zeiss PMQ II spectrophotometer equipped with a cell holder through which water from a thermostated bath was continuously circulated. First-order rate constants were calculated from semilogarithmic plots of the difference between infinite time optical density and optical density at specific times against time. Excellent first-order behavior was observed for all reactions studied. Except for those reaction mixtures containing ionic surfactants, for which additional electrolytes were not added, ionic strength was maintained constant at 0.5 through addition of calculated quantities of KCl. Values of pH were measured employing a Radiometer PHM 26 pH meter.

Activation parameters were calculated from rate constants measured at 20, 30, 40, and 50°. In accord with previous observations,[7] the energy of activation was found to be dependent on temperature and each value was calculated from the following expression[7]

$$E_{act}^{obsd} = [RT_aT_b/(T_b - T_a)] \ln (k_b/k_a) \quad (1)$$

in which k_a and k_b refer to rate constants measured at T_a and T_b, respectively. These values of the energy of activation were subsequently refined using the best value of E_0 and c, obtained by the method of least squares, in which c is the temperature dependence of the activation energy, dE/dT, and E_0 is defined by

$$E_{act}^{obsd} = E_0 + c(T_a + T_b)/2 \quad (2)$$

Values of entropy of activation were then calculated from

$$\ln k_a = \ln (k/h) + \ln (T_a + T_b)/2 + 1 + \Delta S^*/R - E_{act}/RT_a \quad (3)$$

in which k and h are the Boltzman and Planck constants, respectively.

Equilibrium constants for the association of the α,α-dichlorotoluenes with micelles formed from ionic surfactants were estimated from the dependence of rate of hydrolysis on surfactant concentration employing the following expression[11]

$$1/(k_a - k_{obsd}) = 1/(k_a - k_m) + 1/(k_a - k_m)[N/K(C_d - cmc)] \quad (4)$$

in which k_a is the rate constant observed in aqueous solution, k_{obsd} is the rate constant observed at each surfactant concentration, k_m is the rate constant observed at saturating concentrations of surfactant, N is the aggregation number of the micelle, C_d is the concentration of surfactant, cmc is the critical micelle concentration, and K is the equilibrium constant of interest. A value of N equal to 70 was employed in the calculations.

Results

First-order rate constants for hydrolysis of α,α-dichlorotoluene and the *p*-methyl and *p*-chloro derivatives in aqueous solution at 30° and ionic strength 0.5 were mea-

Table I
First-Order Rate Constants for Hydrolysis of α,α-Dichlorotoluenes at 30° as a Function of the Volume Per Cent Dioxane in Water-Dioxane Mixtures[a]

Volume per cent dioxane	Substituent		
	p-Methyl	Hydrogen	p-Chloro
None	13.0	0.17	0.11
5		0.10	
10	5.0	0.045	0.035
15		0.025	
20	2.0	0.015	0.010
30	0.7	0.005	0.003
40	0.08		0.0008
50	0.012	0.00026	0.0016

[a] All rate constants have units of min^{-1}.

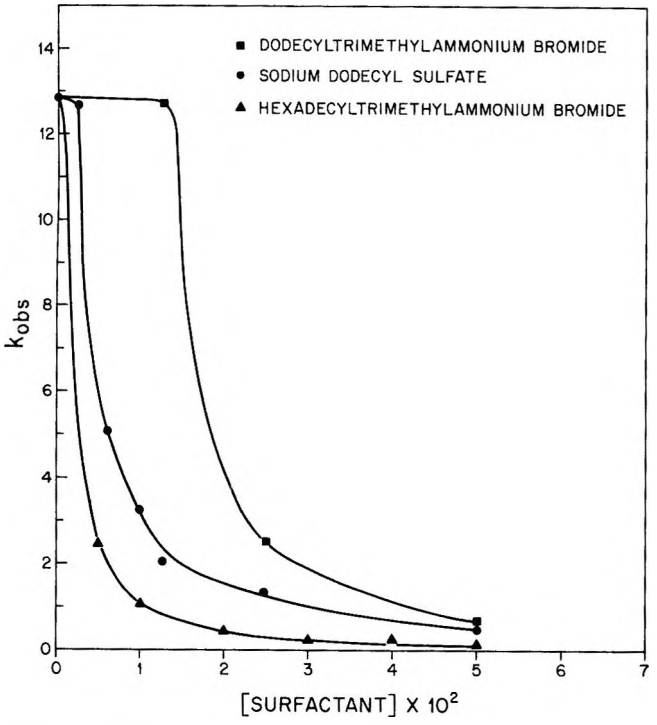


Figure 1. First-order rate constants for hydrolysis of p-methyl-α,α-dichlorotoluene plotted as a function of the concentration of sodium dedecyl sulfate, dodecyltrimethylammonium bromide, and hexadecyltrimethylammonium bromide. All reactions were carried out at 30°; ionic strength was not maintained constant.

sured as a function of pH over the pH range 2–10. In each case, the rate of hydrolysis was observed to be pH independent over the range studied, in accord with previous observations.[6,8] The rate of hydrolysis increases markedly with increasing electron donation from the polar substituent; first-order rate constants measured under these conditions are 0.165, 0.11, and 12.9 min^{-1} for the unsubstituted, p-chloro-, and p-methyl compounds, respectively. Note that the introduction of the mildly electron releasing p-methyl substituent increases the rate of hydrolysis at 30° about 78-fold. On the other hand, the p-chloro substituent has only a small rate-decreasing effect. Hammett plots constructed employing either σ or σ^+ substituent constants are curved.

First-order rate constants for hydrolysis of the α,α-dichlorotoluenes in aqueous dioxane solutions are collected as a function of the volume per cent of dioxane in Table I. In each case, the rate decreases rapidly with increasing dioxane concentration. In 50% aqueous dioxane, rate decreases for the hydrolysis of the p-chloro, unsubstituted,

Table II
The Effect of Ionic Surfactants on the Rate of Hydrolysis of Substituted α,α-Dichlorotoluenes[a]

Surfactant	Concn, M	Substituent		
		p-Chloro	Hydrogen	p-Methyl
Sodium dodecyl sulfate	0.0	0.11	0.17	12.9
	0.005	0.099	0.12	12.7
	0.01	0.043	0.068	3.3
	0.02	0.012	0.037	1.4[c]
	0.04	0.006	0.028[b]	
	0.05	0.0045	0.016	0.5
Dodecyltrimethyl-ammonium bromide	0.0	0.11	0.17	12.9
	0.006	0.10		
	0.012	0.09	0.14[d]	
	0.025	0.008	0.025[b]	2.6
	0.04	0.0049	0.019	
	0.05	0.0034	0.014	0.7
Hexadecyltri-methylammonium bromide	0.0	0.11	0.17	12.9
	0.005	0.089	0.047	2.5
	0.01	0.0036	0.024	1.1
	0.02	0.0036	0.014	0.5
	0.03	0.0021	0.011	0.3
	0.04	0.0011	0.007	0.3
	0.05	0.0010	0.006	0.2

[a] Rate constants have units of min^{-1} and were measured at 30°. [b] 0.03 *M*. [c] 0.025 *M*. [d] 0.01 *M*.

and p-methyl compounds are 680-, 640-, and 1080-fold, respectively, in comparison to rates in water. The data are well-correlated by the equation of Winstein and Grunwald:[12] $\log k/k_0 = mY$. In each case, values of *m* near 1.3 were obtained.

Hydrolysis of α,α-dichlorotoluenes is markedly inhibited by ionic surfactants, both cationic and anionic. In Figure 1, first-order rate constants for the hydrolysis of p-methyl-α,α-dichlorotoluene are plotted as a function of the concentration of sodium dodecyl sulfate, dodecyltrimethylammonium bromide, and hexadecyltrimethylammonium bromide. Comparable data were obtained with the other substrates. Note that each surfactant is an inhibitor for the hydrolysis reaction. The rates become essentially constant at high surfactant concentrations, reflecting complete incorporation of the substrate into the micellar pseudophase. At saturating concentrations of surfactant, rate decreases in the range of 10–100-fold are observed, depending on the nature of the surfactant and substrate. Quantitative data for all substrates studied are collected in Table II.

From the dependence of rate constant on surfactant concentration, approximate equilibrium constants for association of the α,α-dichlorotoluenes with sodium dodecyl sulfate and hexadecyltrimethylammonium bromide micelles were calculated as described above: p-chloro, 42,000 M^{-1}; unsubstituted, 31,000 and 56,000 M^{-1}; p-methyl, 60,000 and 116,000 M^{-1}, respectively. Thus, the equilibrium constants for association of the α,α-dichlorotoluenes are uniformly larger with the more hydrophobic cationic micelles than with the anionic ones.

Values of the entropy of activation for hydrolysis of p-chloro, unsubstituted, and p-methyl-α,α-dichlorotoluenes at 30° were measured as described above. Results obtained are, p-chloro, −7.7 eu; unsubstituted, −11.3 eu; p-methyl, −12.9 eu. Results are considered to be accurate to within ±1.5 eu. These values are consistent with those previously measured for the unsubstituted compound in aqueous ethanol solutions.[7] Clearly, the trend of the values of entropy of activation is contrary to the trend in reactivity. Thus, the greater reactivity of the p-methyl compared to the p-

Table III
Rate Constants for the Hydrolysis of Substituted α,α-Dichlorotoluenes in Aqueous Solution and in the Presence of 0.05 M Hexadecyltrimethylammonium Bromide as a Function of the Concentration of Added Salts[a]

	Additions					
Substrate	None	0.8 M KCl	0.8 M KNO_3	0.05 M HTAB[b]	0.05 M HTAB + 0.8 M KCl	0.05 M HTAB + 0.8 M KNO_3
p-Methyl	12.9	9.0[c]	18.0	0.22	0.10	0.22
Hydrogen	0.17	0.19	0.23	0.006	0.008	0.008
p-Chloro	0.11	0.05	0.075	0.001	0.0003	0.0017[d]

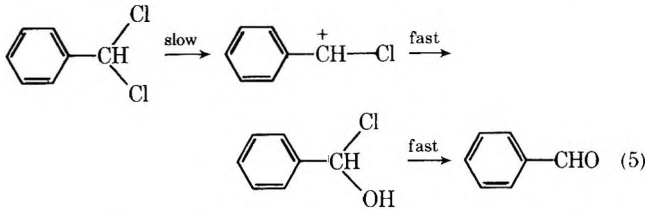
[a] All rate constants have units of min^{-1} and were measured at 30°. [b] Hexadecyltrimethylammonium bromide. [c] 1.0 M KCl. [d] 0.08 M KNO_3.

chloro substrate is a consequence of a lower energy of activation, not a more positive ΔS^*.

Effects of the concentration of salts on the rate of hydrolysis of the α,α-dichlorotoluenes were measured in aqueous solution and in the presence of 0.05 M hexadecyltrimethylammonium bromide. Results are collected in Table III. In all cases, the effects are small. Changes that are observed show no clear trends in terms of nature of the polar substituent or nature of the salt.

Discussion

The most compelling evidence for rate-determining carbon–chlorine bond cleavage for the hydrolysis of α,α-dichlorotoluenes (eq 5) is provided by the work of Tanabe



(5)

and Ido who demonstrated that (i) hydrolysis of α,α-dichlorotoluene in water is pH independent over the range 0–14; (ii) that chloride is a more effective inhibitor than azide or sulfate for the reaction; and (iii) that hydrolysis proceeds more rapidly than exchange of chloride ion into the substrate.[6] This conclusion is supported by the observation that electron-donating polar substituents increase the rate of hydrolysis in aqueous ethanol mixtures[8] although it did not prove possible to correlate the rate constants with a linear free energy relationship.

Results reported in this manuscript corroborate this conclusion. For the three substrates studied, rate constants independent of pH have been observed over the range investigated, confirming the absence of detectable acid or base catalysis. The effect of polar substituents on rate provides strong evidence for a carbonium ion mechanism. Specifically, the striking rate-promoting effect of the p-methyl substituent, in both water and 50% dioxane, argues for an electron-deficient center in the transition state. The evidence is less compelling in the case of the p-chloro compound, which is only slightly less reactive than the unsubstituted derivative. The effect of methyl group substitution on reactivity is more pronounced than in the case of acid-catalyzed hydrolysis of benzaldehyde acetals[13–17] for which rate-determining carbonium ion formation has been established.[1–3]

The powerful inhibition of hydrolysis of α,α-dichlorotoluenes by dioxane (Table I) provides additional evidence in favor of rate-determining carbonium ion formation for these reactions. Since the transition state is more polar than the ground state, it follows that less polar solvents will inhibit the reaction. The large value of m derived from use of the equation of Winstein and Grunwald suggests that the transition state has considerable polar character. That is, rupture of the carbon–chlorine bond may be nearly complete in the transition state.

The marked inhibition of hydrolysis of α,α-dichlorotoluenes by ionic surfactants, independent of charge (Figure 1, Table II), is also consistent with a carbonium ion mechanism. It is known that the micellar surface is substantially less polar than is the bulk phase[18,19] and hence, according to the argument presented above, incorporation of the substrates onto this surface should retard the reaction. That the effect observed is predominantly a result of the lowered polarity at the micellar surface rather than electrostatic interactions is established both by the fact that inhibition is independent of the nature of the micellar surface charge and is little affected by the addition of salts (Table III) which results in an increase in the extent of micellar charge neutralization. The inhibition of hydrolysis of α,α-dichlorotoluenes by sodium dodecyl sulfate is in marked contrast to catalysis of hydrolysis of acetals and ortho esters elicited by the same surfactant.[14,16,19,20] The distinctive behavior is undoubtedly the consequence of the cationic nature of the transition state for hydrolysis of acetals and ortho esters, on the one hand, and the zwitterionic nature of the transition state for hydrolysis of the α,α-dichlorotoluenes, on the other.[17]

There is some reason to believe that the carbonium ion derived from the α,α-dichlorotoluenes is not highly selective in its reactions with nucleophiles. The small salt effects observed in this work suggest that it is difficult to trap this carbonium ion with chloride ion or nitrate ion. Moreover, Tanabe and Ido found little effect on the rate of hydrolysis of α,α-dichlorotoluene following addition of azide, sulfate, piperidine, or thiophenol.[6] These results suggest that the carbonium ion reacts with the first nucleophile that it encounters, usually water. In contrast, it is quite possible to trap the more stable carbonium ion formed in the hydrolysis of ortho esters.[21]

Acknowledgment. The support of CONICIT, Grant DFS1028, is gratefully recognized.

Registry No.—α,α-Dichlorotoluene, 98-87-3; p-methyl-α,α-dichlorotoluene, 23063-36-7; p,α,α-trichlorotoluene, 13940-94-8; sodium dodecyl sulfate, 151-21-3; dodecyltrimethylammonium bromide, 1119-94-4; hexadecyltrimethylammionium bromide, 57-09-0.

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α,α′-Dibromocycloalkanones. Preparation and Conformation

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The stereoisomeric α,α′-dibromocycloalkanones from cyclohexanone to cyclododecanone have been prepared as far as this has been possible. Where known (n = 6, 10, 11, 12, 13) the cis (meso) isomers have higher melting points and higher ir carbonyl stretch frequencies and are more polar as well as less soluble than the trans (*dl*) analogs which are considered to be conformationally more mobile. Since the meso:*dl* ratio of the C_{11} and especially C_{12} dibromocycloalkanone at equilibrium approaches that of the most simple acyclic analog, *viz.*, 2,4-dibromo-3-pentanone, open-chain behavior and relatively free rotation in the larger rings are suggested.

As a class of compounds α,α′-dibromocycloalkanones have been investigated by a wide range of physical[1] and theoretical techniques[1a] and have also served as intermediates in synthesis.[2] A new synthetic application which has considerable potential for growth is their use as precursors of metal oxyallyl, especially zinc oxyallyl species as described in another paper.[3] From the very beginning of our work it seemed desirable to gain conformational insight into these compounds which would help us to understand differences in reactivity as well as steric and mechanistic features of the zinc-induced dehalogenation. Accordingly, we have prepared and isolated, as far as this has been possible, all stereoisomeric α,α′-dibromocycloalkanones from C_6 to C_{12} and have investigated their physical and spectroscopic properties.

Discussion

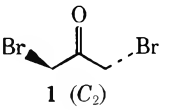
The compounds, together with their melting points and epimeric ratios at equilibrium are listed in Table I, which also indicates the earlier contributions of other workers, notably Corey,[4] Borsdorf, *et al.*,[5] and Garbisch.[2b]

One can see immediately that the diastereoisomeric ratio for the C_{11} and especially the C_{12} isomers approaches that of the most simple acyclic disecondary dibromo ketone, *viz.*, 2,4-dibromo-3-pentanone. It has been shown quite independently that these compounds resemble each other in forming a W cation on dehalogenation.[3] Apparently, in choosing their optimum conformation the C_{11} and C_{12} stereoisomers are relatively free to rotate and, in fact, approach the behavior of the acyclic model. For this reason we prefer the terms meso and *dl* to cis and trans when dealing with the C_{11}, C_{12}, and also C_{13} dibromocycloalkanones.[6]

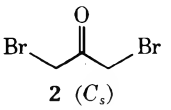
The changeover from large to medium ring behavior occurs in the 10-membered system where the trans epimer is now somewhat more stable than the cis analog. Of the six possible C_7–C_9 dibromocycloalkanones only the trans isomers have so far been isolated, also after attempted epimerization.[16] Clearly, in this case the cis epimers must be markedly less stable (>2 kcal/mol), a fact to be discussed below.

Melting Points. The melting of solids may be treated thermodynamically, $\Delta G = \Delta H - T\Delta S$. At equilibrium, $\Delta G = 0$ and $T_m = \Delta H_m/\Delta S_m$. If the heat of fusion ΔH_m does not change much, as is often the case for related compounds, a high entropy of fusion ΔS_m entails a low melting point *vice versa*. Now ΔS_m is largely determined by the gain of conformational mobility in the liquid state, the conformation in the crystal lattice being unique.[7] On this model it is understandable that *cis*-2,6-dibromocyclohexanone melts higher than the trans form, because in the former isomer, population of the a,a conformer in the liquid state is not very favorable, while the latter may undergo degenerate interconversion (a,e ⇌ e,a) and hence gain conformational mobility on melting (see Figure 1). For the same reason the *dl* isomers of C_{11} and C_{12} (which melt below the corresponding meso isomers) are considered to be conformationally more mobile and to have less well-defined energy wells than the meso analogs. Again, this conclusion accords with other evidence, such as the reduced polarity and broader ir carbonyl peaks (CCl_4 solvent, Table II) of the *dl* isomers. Of all the α,α′-dibromocycloalkanones which we have investigated, *trans*-2,10-dibromocyclodecanone is perhaps most interesting, because it is the only compound (n = 6–13), which is not a solid at room temperature. In fact, even on further cooling we never succeeded to crystallize the compound which remained a yellow liquid after redistillation at reduced pressure. On these grounds and also on the basis of chemical evidence[3] *trans*-2,10-dibromocyclodecanone appears to be conformationally less rigid, in contrast to cyclodecanone itself and its simpler derivatives, which have been shown to have a relatively well-defined, diamandoid conformation, similar to cyclohexane and adamantane.[8] Assuming that the trigonal carbon appears as a type III atom so as to remove intraannular repulsion,[8] one can see that the bromine atoms of the trans isomer are forced to adopt rather unfavorable positions, reminiscent of a syn-diaxial relationship in cyclohexanone (Figure 2); the resulting repulsion of unshared electron pairs on bromine might also account for the yellow color of the compound. Whatever further conformational details may come to light we believe that the structure of *trans*-2,10-dibromocyclodecanone is not a good model for that of the parent ring ketone.

The postulated greater conformational mobility of the trans (*dl*) isomers (n = 6, 10–12) is also manifest in physical properties other than melting points. Thus, they showed a generally reduced polarity and tended to be more soluble, not only in the mother liquors during preparation but also in benzene and less polar hydrocarbons. Furthermore, the cis (meso) C_{10}, C_{11}, and C_{12} dibromocycloalkanones could be grown without effort to long, colorless needles, whereas the *dl* C_{11} and C_{12} forms tended to form microcrystals. Note also that the trans isomers have the lower ir carbonyl stretch frequency (Table II). Presumably, on a time-averaged basis they have C_2 symmetry **1**, while the cis isomers have C_s symmetry. As a consequence, dipole–dipole repulsion of the electronegative oxygen with the flanking bromines in the cis isomers **2** and partial cancelation of the C–Br dipoles in the trans isomers **1** conspire to



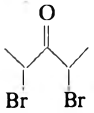
1 (C_2)



2 (C_s)

increase the polarity of the *cis*-dihalo ketones. It should be mentioned that from a synthetic viewpoint the conformationally more mobile trans isomers—at least in the case of

Table I
α,α'-Dibromocycloalkanones from Cyclohexanone to Cyclododecanone

No. of carbons	Diastereoisomer	Mp, °C	Lit. mp, °C	Cis:trans ratio at equil	Lit. ref or elemental anal. (%)	Registry no.
6[a]	Cis	112	112	0.18	4	16080-75-4
6	Trans	35	36		4	16080-74-3
7	Trans	70	70	0	5	18315-97-4
8	Trans	82	82	0	5	16110-80-8
9[b]	Trans	51		0	Calcd for $C_9H_{14}OBr_2$: C, 36.27; H, 4.73. Found: C, 36.22; H, 4.74	52928-61-7
10	Cis	55		~0.5	Calcd for $C_{10}H_{16}OBr_2$: C, 38.48; H, 5.17. Found: C, 38.39; H, 5.02	52906-73-7
10	Trans	Bp 60–64° (0.001 mm)			Calcd for $C_{10}H_{16}OBr_2$: 38.48; H, 5.17. Found: C, 38.28; H, 5.11	52949-45-8
11	Meso	80	80	1.6	2b	19914-86-4
11	*dl*	54	56		2b	19914-87-5
12	Meso	126	126	3.8	2b	19914-84-2
12	*dl*	48	48		2b	19914-85-3
13	Meso	110				52906-74-8
	Meso			~5.0[c]		51513-32-7
	dl					51513-33-8

[a] 2,5-Dibromocyclopentanone, mp 67°, has also been obtained; see Experimental Section. [b] 2,2-Dibromocyclononanone, mp 69°, is formed as a major by-product. [c] Determined by $NaBH_4$ reduction into the diastereoisomeric dibromohydrins according to ref 2b.

Table II
Carbonyl Stretch Frequencies (cm^{-1}) of α,α'-Dibromocycloalkanones[a]

No. of carbons	Parent cycloalkanone Mull or smear	*cis*-Dibromocycloalkanone Mull or smear	*cis*-Dibromocycloalkanone CCl_4	*trans*-Dibromocycloalkanone Mull or smear	*trans*-Dibromocycloalkanone CCl_4
6	1715	1745	1755 v (1713)	1739 v	1739 v
7	1704	1721	1731 v		
8	1702 b22	1718	1727 v		
9	1702	1721	1719 b10		
10	1705	1721 b16	1731 v	1704 v	1708
11	1707	1730	1727 v	1712	1710 b8
12	1712	1727	1728 v	1713 v	1709 b8
13	1713		1716 v		

[a] The spectra were recorded on a Perkin-Elmer grating spectrometer, Model 257. The carbonyl regions were expanded so that 1 cm corresponded to 20 cm^{-1}. Abbreviations: v, sharp; b22, broad, approximate spread in cm^{-1}.

trans-2,10-dibromocyclodecanone[3]—seem to be more suitable for generating zinc oxyallyl, the formation of which is considered to require quasiaxial departure of bromine to optimize orbital overlap.

Why are the cis isomers (n = 7–9) as yet inaccessible by epimerization? Cycloheptane[9] and presumably cycloheptanone as well prefer the C_2 conformation (Figure 3) allowing the bromines of the observed trans isomer to occupy quasiequatorial positions at the periphery.[10] Similarly, the tendency to maintain time-averaged C_2 symmetry such that conformational imperfections may travel easily around the ring[7c] could account for our failure to obtain *cis*-2,8-dibromocyclooctanone and the cis C_9 derivative. Significantly, where cis and trans isomers do exist (n = 6, 10–12) the difference in melting points is apparently smaller in the odd-membered (n = 11) ring (Figure 1).

Attempts to analyze the pmr spectra of the C_7–C_{12} dibromocycloalkanones were not very successful, even after decoupling experiments, simulation of spectra by computer, and cooling of the solution down to the lowest possible temperatures (*ca.* −110°).[11] However, it is worthy of mention that the meso isomers of those α,α'-dibromocycloalkanones which displayed open-chain behavior (C_{11}, C_{12}, and also C_{13}) showed the CHBr quartet at lower field than the corresponding *dl* analogs (Table III). Consistently, *meso*-2,4-dibromo-3-pentanone had its methine quartet centered on δ(TMS, CCl_4) 7.01 ppm, while the quartet of the *dl* diastereoisomer appeared at higher field (δ 6.48). This finding is in accord with averaged C_s symmetry 2 for the more polar meso isomer and might serve as a criterion for the distinction of *dl* and meso diastereoisomers of comparable mobile systems.

Table III
Pmr Data for α,α'-Dibromocycloalkanones[a]

Compd	Chem shift of CHBr proton, δ (TMS, $CDCl_3$), ppm	Obsd sepn of of signals, Hz
C_7 trans	4.72	4.9, 5.3, 4.9
C_8 trans	4.68	5.9, 1.6, 1.6, 1.5, 6.0
C_9 trans	4.60	7.45, 7.5
C_{10} cis	4.90	4.75, 0.7, 4.25, 5.0
C_{10} trans	4.95	6.5, 6.4
C_{11} meso	4.81	3.75, 6.0, 3.75
C_{11} *dl*	4.70	4.8, 4.4, 4.8
C_{12} meso	5.02	3.75, 5.0, 3.75
C_{12} *dl*	4.62	4.6, 6.0, 4.6

[a] Spectra were recorded on a Varian HA 100 nmr spectrometer using 0.1 *M* $CDCl_3$ solutions containing 5% TMS as internal standard.

Experimental Section

Preparation of α,α'-Dibromocycloalkanones. The preparation and properties of some α,α'-dibromocycloalkanones have already been reported (see Table I). A general procedure is as follows. Cycloalkanone (1 mol) was stirred rapidly in anhydrous ether (300 ml) at 0–5°, 1 drop of bromine being introduced. Only after

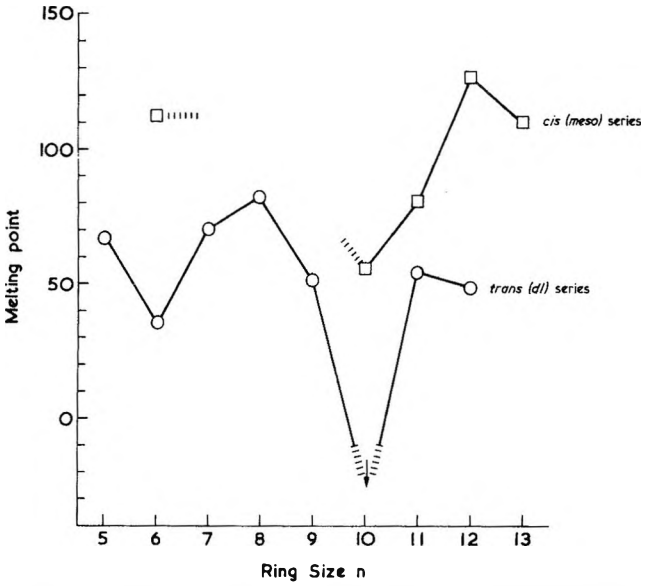


Figure 1. Melting points of stereoisomeric α,α′-dibromocycloalkanones as a function of ring size.

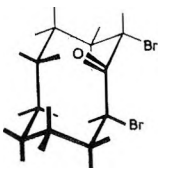


Figure 2. Dunitz conformation of *trans*-2,10-dibromocyclodecanone.

Figure 3. C_2 conformation of cycloheptanone.

the color of bromine had disappeared was the bulk of the bromine (1 mol) added so that the temperature did not exceed 10°. The reaction solution was allowed to warm to 25–30° and more bromine (1 mol) was added slowly. After being stirred for 1 hr further, the mixture was washed with 2% aqueous $Na_2S_2O_3$, 10% Na_2CO_3, and finally water. The solution was dried and the solvent was removed until crystallization occurred.

Special Procedures. 2,5-Dibromocyclopentanone (N. H. Burt). The bromination was carried out at 3° in glacial acetic acid, the HBr formed being blown out by a stream of nitrogen. The mixture was poured onto ice, neutralized with $NaHCO_3$ to pH 5, and extracted with CCl_4. The organic layer was washed with dilute $NaHCO_3$, dried ($MgSO_4$), filtered, and cooled for several hours to *ca.* −25°, giving a pale yellow oil which on fractional crystallization from *n*-pentane–CCl_4 (50:50 v/v) followed by repeated recrystallization from pentane yielded **2,5-dibromocyclopentanone:** white needles stable in air; mp 67°; ir (CCl_4, cm^{-1}) 1767 v; pmr δ (TMS, CCl_4) 2.5 (m, 4 H), 4.27 ppm (complex m, 2 H). Computer simulation of the spectrum, which, however, cannot stand on its own as a piece of evidence, suggests that the compound is the trans isomer.[12]

cis- **and** *trans*-**2,6-Dibromocyclohexanone.**[4] The reaction mixture was kept as dilute as possible to minimize formation of a wine red solution. After cooling to −78° the cis isomer was filtered off and recrystallized several times from a mixture of ligroin–diethyl ether: mp 112° (30%). The mother liquors were pooled, concentrated to *ca.* 50 ml, and stored at 0° over several days to yield another batch of product. Continued treatment in this way gave *cis*-2,6-dibromocyclohexanone in *ca.* 45% total yield. The equilibration of the cis and trans isomer was conveniently carried out at 25° for 4–6 hr using solvent ether saturated with anhydrous HBr and also anhydrous HCl.[13]

trans-**2,7-Dibromocycloheptanone.**[5] Recrystallization from petroleum ether (bp 80–120°) followed by treatment with activated charcoal in ether gave *trans*-2,7-dibromocycloheptanone: mp 70°; colorless solid (48% after purification).

trans-**2,8-Dibromocyclooctanone.**[5] The compound was obtained as described for the lower homolog and had mp 82° after recrystallization.

trans-**2,9-Dibromocyclononanone and 2,2-Dibromocyclononanone.** Careful bromination at 0° gave two hand-separable crystalline forms from *n*-pentane in about 40% yield after purification: *trans*-2,9-dibromocyclononanone, rhomboids, mp 51°, and needles of a second isomer which on the basis of its pmr and mass spectra was 2,2-dibromocyclononanone,[14] mp 69°. *Anal.* Calcd for $C_9H_{14}OBr_2$: C, 36.27; H, 4.73. Found: C, 35.75; H, 4.60.

cis- **and** *trans*-**2,10-Dibromocyclodecanone.** Fractional crystallization from *n*-pentane yielded solid *cis*-**2,10-dibromocyclodecanone,** mp 55°. The filtrate was cooled to −78° for several hours to yield an oil, which was distilled and gave *trans*-**2,10-dibromocyclodecanone** as a stable yellow oil, bp 60–64° (0.001 mm). On cooling to −78° the oil set to a solid glass. The combined yield of the two stereoisomers, which were isolated in a ratio of 35:65, amounted to *ca.* 65%.

meso- **and** *dl*-**2,11-Dibromocycloundecanone.**[2b] The bromination yielded two forms which were easily separated by fractional crystallization from ether–*n*-pentane to give *meso*-2,11-dibromocycloundecanone, mp 80°, and *dl*-2,11-dibromocycloundecanone, mp 54°, in 85% overall yield.

meso-**2,12-Dibromocyclododecanone.**[2b] During bromination it was often found that the predominant meso isomer, mp 126°, separated as a solid. If so, it was filtered off before bromination was resumed. The *dl* isomer was obtained by epimerization with anhydrous acid.

Preparation of Parent Cycloalkanones. Cyclononanone, cyclodecanone, and cycloundecanone were synthesized in a number of ways,[15] the sequence of Garbisch[2b] being found to be most satisfactory.

Acknowledgments. We thank Mr. N. H. Burt and Dr. C. Chassin for experimental contributions and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—Dibromocyclopentanone, 53778-21-5; 2,2-dibromocyclononanone, 52951-33-4.

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(11) Further details: J. G. Vinter, Ph.D. Thesis, University of London, 1973.
(12) The reaction of cyclopentanone with bromine has been reported to give a dibromocyclopentanone $C_5H_6OBr_2$ of mp 68–69°; see I. V. Machinskaya and A. S. Podberezina, *Zh. Obshch. Khim.*, **28,** 1501 (1958); *Chem. Abstr.*, **53,** 11841 (1959).
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(16) **Note Added in Proof.** The preparation of both *cis*-2,5-dibromocyclopentanone and *cis*-2,7-dibromocycloheptanone has recently been implied, although no experimental details have been given; see R. H. Prager and J. M. Tippett, *Tetrahedron Lett.*, 5199 (1973). We believe that the assignment of at least the seven-membered derivative must be reversed.

Synthesis of Phthalimidines from Aromatic Dicarbonyl Compounds

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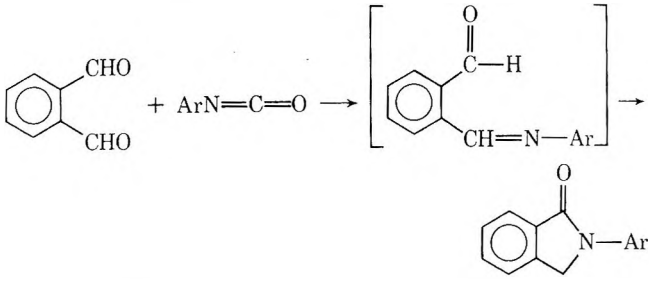
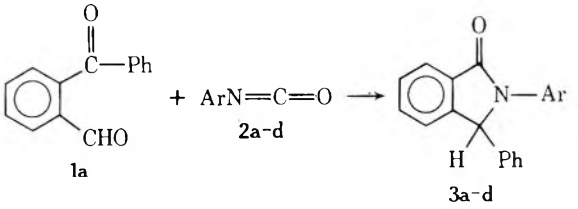
The reaction between *o*-benzoylbenzaldehyde (**1a**) and aromatic isocyanates (**2a–d**) afforded 2,3-disubstituted phthalimidines **3a–d** in good yield, which would be formed *via* *o*-benzoylbenzylideneaniline intermediate followed by migration of phenyl group. The same product **3a** was obtained by the reaction using 1a and aniline. On the other hand, no reaction was observed between *o*-carbetoxybenzaldehyde (**23**) and **2a**, but the reaction of **23** with aniline gave o-carbetoxybenzylideneaniline (**24**) and 3-anilino-2-phenylphthalimidine (**21a**) in 83 and 7% yield, respectively.

Previously we reported a synthetic method for *N*-arylphthalimidines by the reaction of an aromatic isocyanate and phthalaldehyde.[1] In the present paper, we report the reactions of isocyanates with aromatic dicarbonyl compounds and a new synthetic method for 2,3-disubstituted phthalimidines.

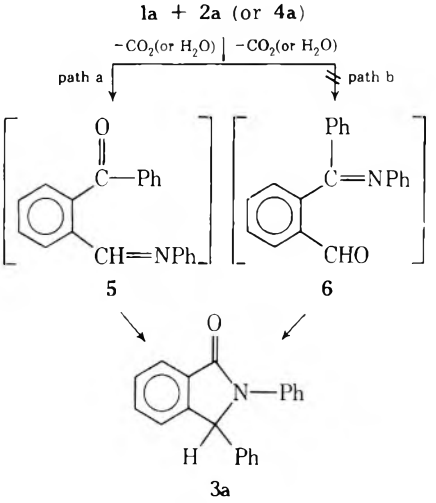


o-Benzoylbenzaldehyde. Treatment of *o*-benzoylbenzaldehyde (**1a**) with an equimolar amount of phenylisocyanate (**2a**) at 200° for 15 hr afforded 2,3-diphenylphthalimidine (**3a**) in 67% yield. The reaction of **1a** with other isocyanates gave phthalimidines **3b–d**. Both the ir (C=O at 1680 cm^{-1}) and nmr (singlet for CH at δ 6.05) spectra of **3a** are fully consistent with the structure; **3b–d** also showed nmr singlets at δ 5.98–6.02. The mass spectrum of **3a** exhibited a molecular ion peak at *m/e* 285, in accordance with a general formula $C_{20}H_{15}ON$, and the fragmentation pattern was in agreement with phthalimidine structure.



2a and 3a, Ar = C_6H_5
2b and 3b, Ar = *m*-$CH_3C_6H_4$
2c and 3c, Ar = α-naphthyl
2d and 3d, Ar = β-naphthyl

Chart I

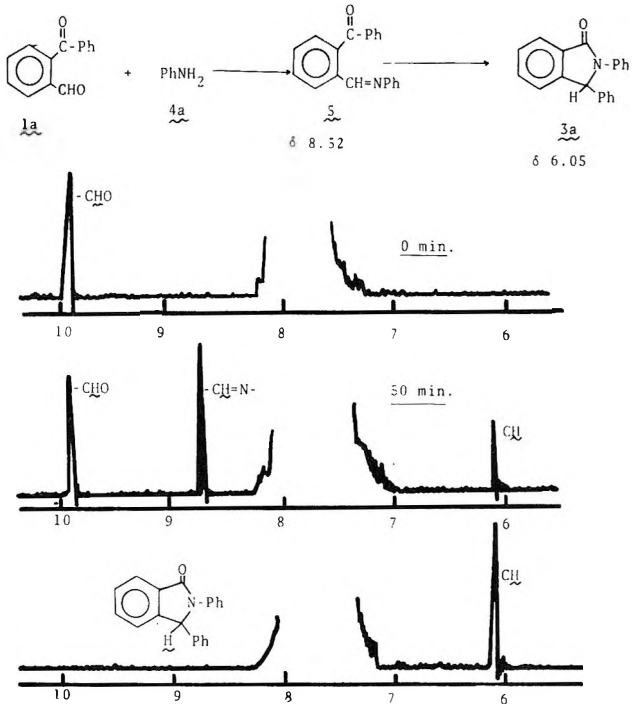


As expected, treatment of **1a** with aniline (**4a**) gave **3a** in 65% yield. These observations suggest that the reaction be-

Table I
The Reaction of Aromatic Isocyanate with *o*-Benzoylbenzaldehyde[a]

Products	Reaction time, hr[b]	Yield, %[c]	Mp, °C	Ir(C=O),[d] cm^{-1}	λ_{max}, nm	Nmr, δ CH	Nmr, δ CH_3	Nmr, δ Aromatic
3a	15	67	192–194	1680	275	6.05		7.0–8.1
3b	16	54	175–176	1680	275	6.02	2.25	6.7–8.0
3c	19	84	190–191	1705	275, 283, 293	5.98		6.8–8.2
3d	19	81	200–201	1680	260, 268, 283, 300	5.99		6.7–8.2
3e	9	52	190–190.5	1680		6.03	2.24	7.0–8.1

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds. [b] The reaction was monitored by ir. [c] Based on isocyanate. [d] Nujol mull.



Time	Relative Intensity CHO	-CH=N-	CH
0 min.	1	0	0
17 min.	1	2	0.2
50 min.	1	3.5	0.6

Figure 1. Nmr spectra of the reaction of **1a** with aniline at room temperature in $CDCl_3$.

tween **1a** and **4a** proceeds *via* a similar intermediate as that of isocyanates, as shown in Chart I.

The formally different pathways, A and B, can be envisaged for the reaction of isocyanate (or aniline) with *o*-benzoylbenzaldehyde (**1a**) studied in this work: *i.e.*, the reaction of isocyanate (or aniline) with (A) aldehyde function of **1a**, followed by the cyclization accompanied with migration of phenyl group, (B) ketone function of **1a**, followed by the cyclization accompanied with migration of hydrogen. Since ketones are generally much less reactive than aldehydes in the formation of imines,[2] path A should be followed. To verify that the reactions of **1a** with isocyanate (and/or aniline) go through path A, the reactions were monitored by nmr. The nmr spectra showed the proton resonances at δ 8.47 (reaction with isocyanate) and δ 8.52 (reaction with aniline), both being assigned to the CH=N proton (Figures 1 and 2), but did not show any aldehyde proton signal for the intermediate **6**. Based on these observations, the formation of phthalimidines **3a–d** from aldehyde **1a** and isocyanates **2a–d** (and/or aniline) may be accounted for by a pathway in which the initial loss of $CO_2(H_2O)$, resulting in the formation of *o*-benzoylbenzylidene aniline (**5**) (not *o*-formylbenzophenone anil (**6**)), is followed by the cyclization with concerted migration of phenyl group (path A, not path B).

To clarify the migration mechanism of phenyl group, we studied the reaction between *o*-(p-toluoyl)benzaldehyde (**1b**) and **2a**. When a mixture of **1b** and **2a** was heated at 200° for 9 hr, 2-phenyl-3-(*p*-tolyl)phthalimidine (**3e**) was obtained in 52% yield (neither *m*-tolyl- **3f** nor o-tolylphthalimidine **3g** were obtained). The structure of **3e** was confirmed by ir, nmr, and carbon-13 FT nmr (Table II[3] and Figure 3) spectra. The carbon-13 nmr spectrum of **3e** showed two singlets at δ 126.802 and 128.804, which were

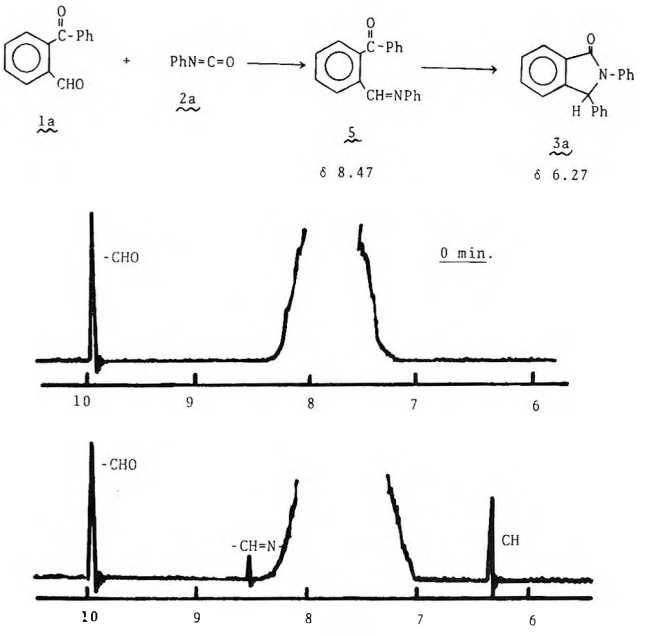
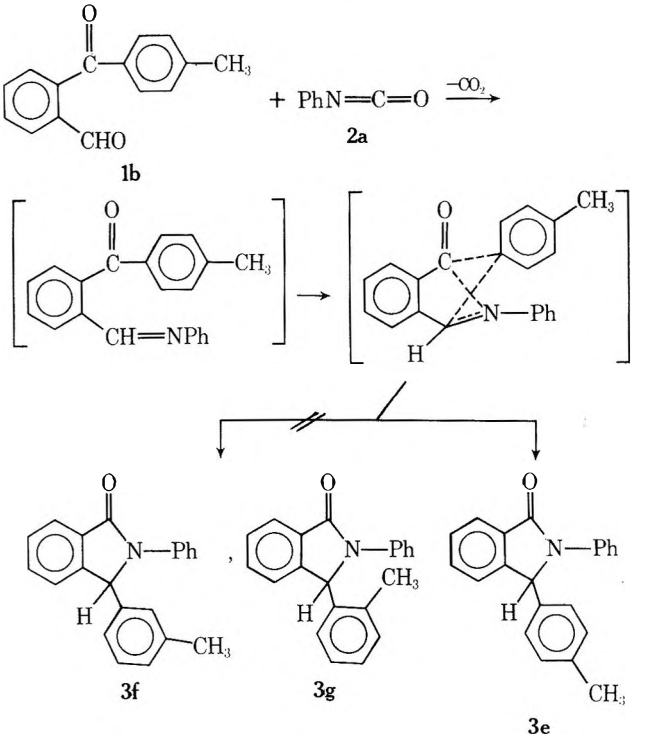


Figure 2. Nmr spectra of the reaction of **1a** with **2a** at 160° in PhN=C=O without solvent.

Chart II



assigned to C-16,20 and C-17,19 by comparison with the carbon-13 nmr spectra of 2-phenylphthalimidine and 2,3-diphenylphthalimidine, as shown in Figure 3. These observations suggest each pair of carbons, C-16 and -20, C-17 and -19, being equivalent, respectively. Therefore the site of the methyl group was determined as being in the para position. Based on this result, we supposed that the reaction may occur *via* bridged intermediate or a concerted process as shown in Chart II, but no other evidence of concerted mechanism has been obtained.

Phthalaldihydic Acid. The reaction of phthalaldehydic acid (**8**) with **2a** afforded 3-hydroxy-2-phenylphthalimidine (**9**, 30%), 3-*N*,*N*′-(diphenylureido)-2-phenylphthalimidine (**10a**, 12%), phthalic anhydride (**11**, trace), *N*-phenylphthalimide (**12**, 15%), *N*,*N*′-diphenylurea (**13**,

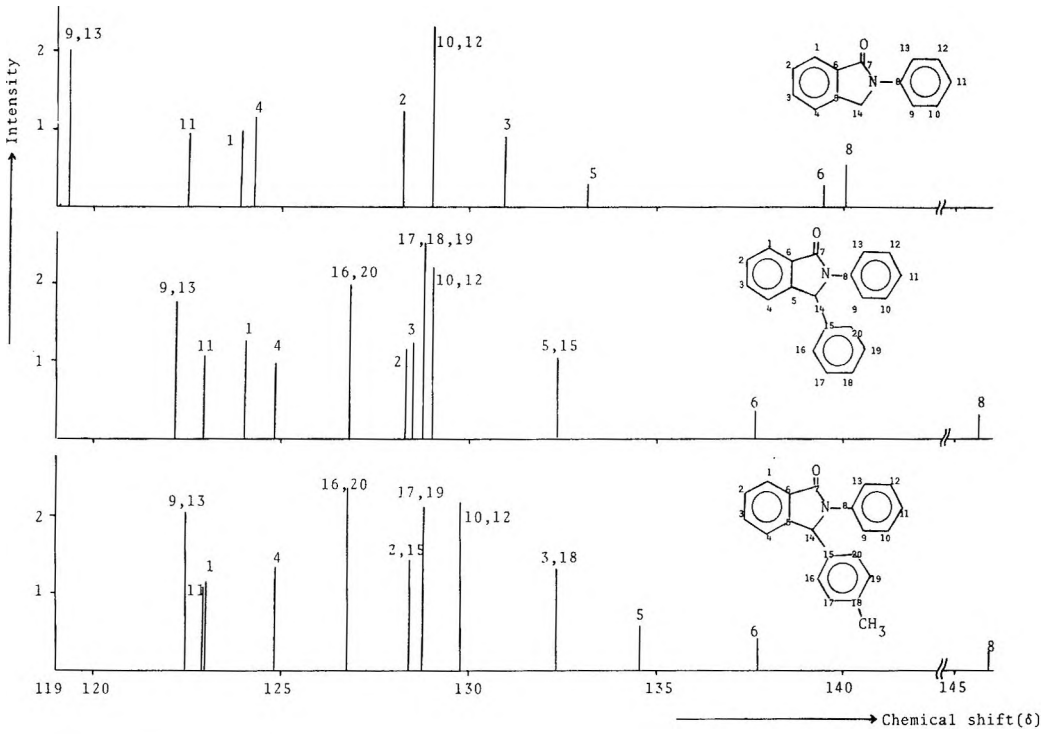
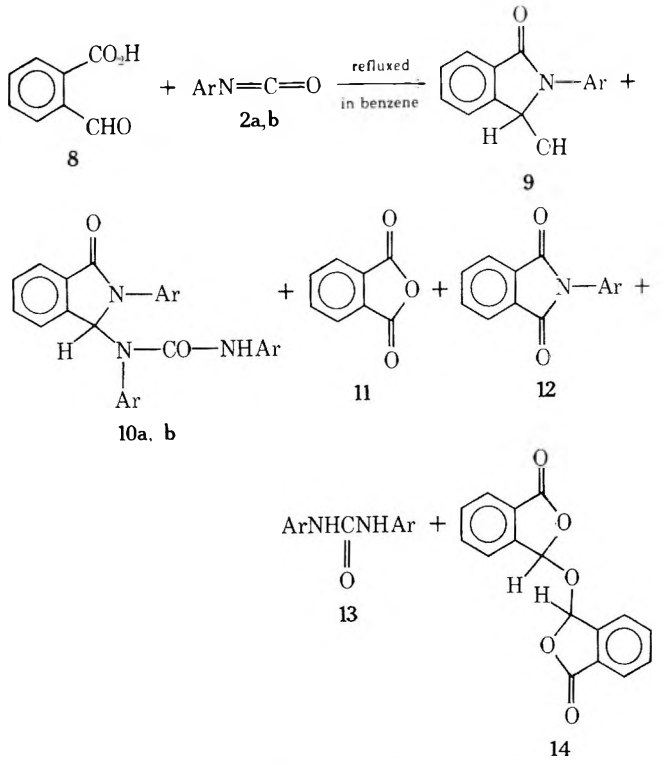


Figure 3. The carbon-13 FT nmr spectra of phthalimidines.

Chart III

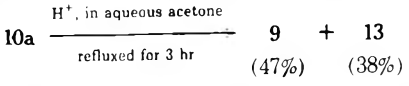


a, Ar = C_6H_5; b, Ar = m-$CH_3C_6H_4$

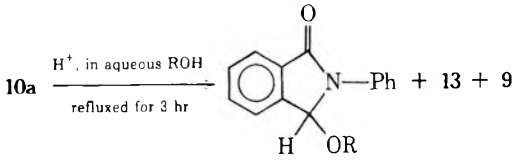
trace), and 3,3′-oxydiphthalide (**14**, trace), as shown in Chart III.

The structure of **10a** was established by the following spectral data and chemical reactions. Product **10a** displayed a NH absorption band at 3300 cm^{-1} and two carbonyl absorptions at 1700 and 1670 cm^{-1}. Its nmr spectrum contained two singlets and a multiplet at δ 6.37, 8.8, and 6.4–7.8 ppm in the ratio of 1:1:19 which were assigned to CH, NH, and aromatic protons, respectively. Furthermore, the mass spectrum of **10a** showed a molecular ion peak at m/e 419 and fragmets at m/e 300, 299, and 208.

Upon the treatment of **10a** with aqueous acetone in the presence of hydrochloric acid, phthalimidine **9** and diphenylurea **13** were obtained in 47 and 38% yield, respectively.



When **10a** was refluxed in aqueous methanol in the presence of HCl, 3-methoxy-2-phenylphthalimidine (**15a**) and **13** were major products (81 and 98% yield, respectively).

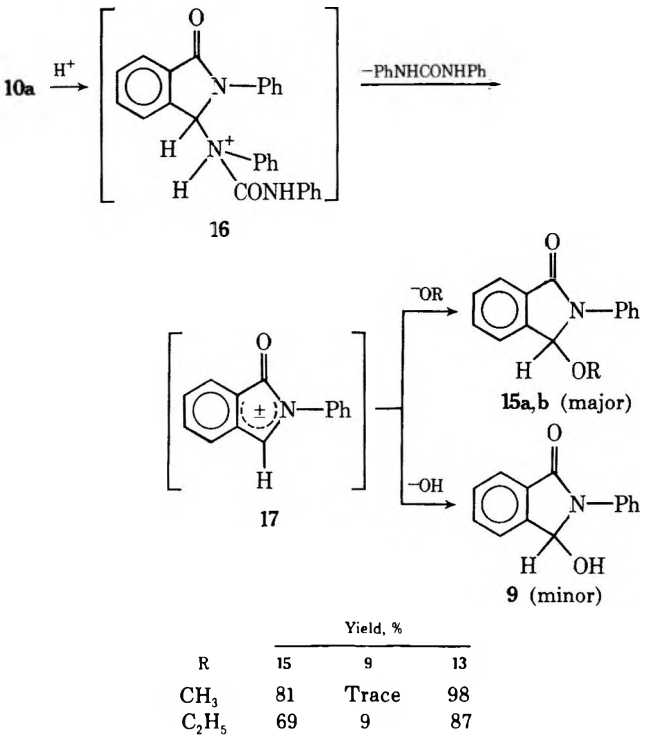


15a, R = CH_3
b, R = C_2H_5

The formation of **9**, **13**, and **15a,b** would be initiated by the protonation at the ureido nitrogen (giving the intermediate **16**), as shown in Chart IV, followed by the elimination of diphenylurea. The intermediate **17** derived from **16** might behave as a soft acid[4] due to the delocalization of positive charge. It would then be attacked by $^-$OR, a rather soft base compared with $^-$OH, to afford **15a,b**, predominantly.

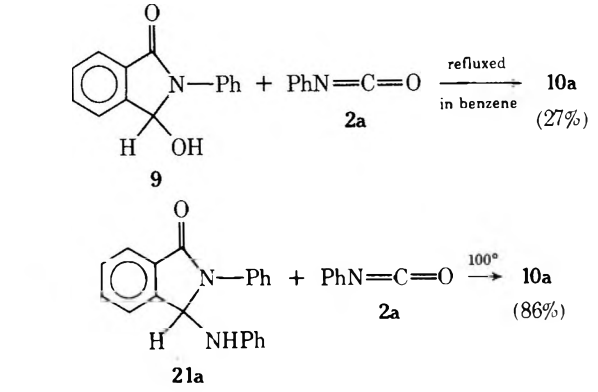
Phthalaldehydic acid is often represented as **8** with an aldehyde and an acid group. But the tautomeric 3-hydroxyphthalide (**18**) has also been suggested. The tautomeric material has been reported to exist in both the open and ring-closed forms depending upon solvent and temperature.[5] Therefore, two possible routes (paths A and B) leading to **10a,b** may be proposed as shown in Chart V. The formation of amide **20** from its precurser **19** is readily explained by the addition reaction of acid into isocyanate (**8** → **19** → **20**, path A). 3-Hydroxyphthalimidine **9** derived by the cyclization of **20** could give intermediate **21**, which would undergo further reaction with isocyanate to produce **10a,b**. Since with path B it is difficult to explain the formation of **9** and **12**, path A may be more preferable. Path A is also supported by the reaction of **2a** with **9**. Refluxing of **2a** with **9** in

Chart IV



R	Yield, % 15	9	13
CH_3	81	Trace	98
C_2H_5	69	9	87

benzene gave **10a** in 27% yield. Furthermore, when **2a** was heated with 3-anilino-2-phenylphthalimidine (**21**) prepared independently,[6] at 100° for 3 hr, **10a** was isolated in 86% yield.



Ethylphthalaldehydate. Phenylisocyanate was found not to react with ethylphthalaldehydate (**23**). No change in ir spectra was observed, even when the two were mixed and allowed to stand at 250° for 45 hr.

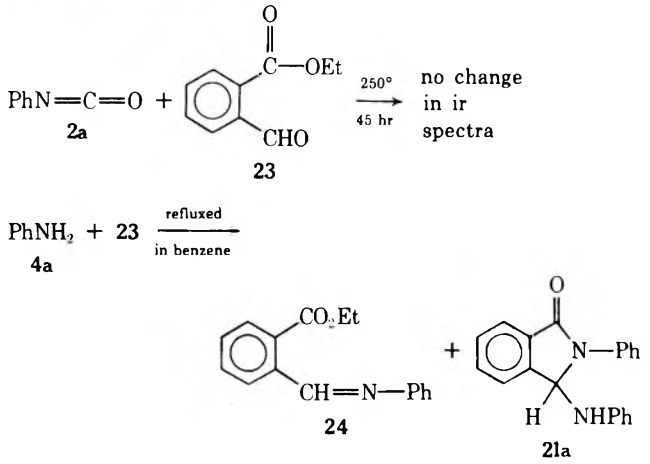
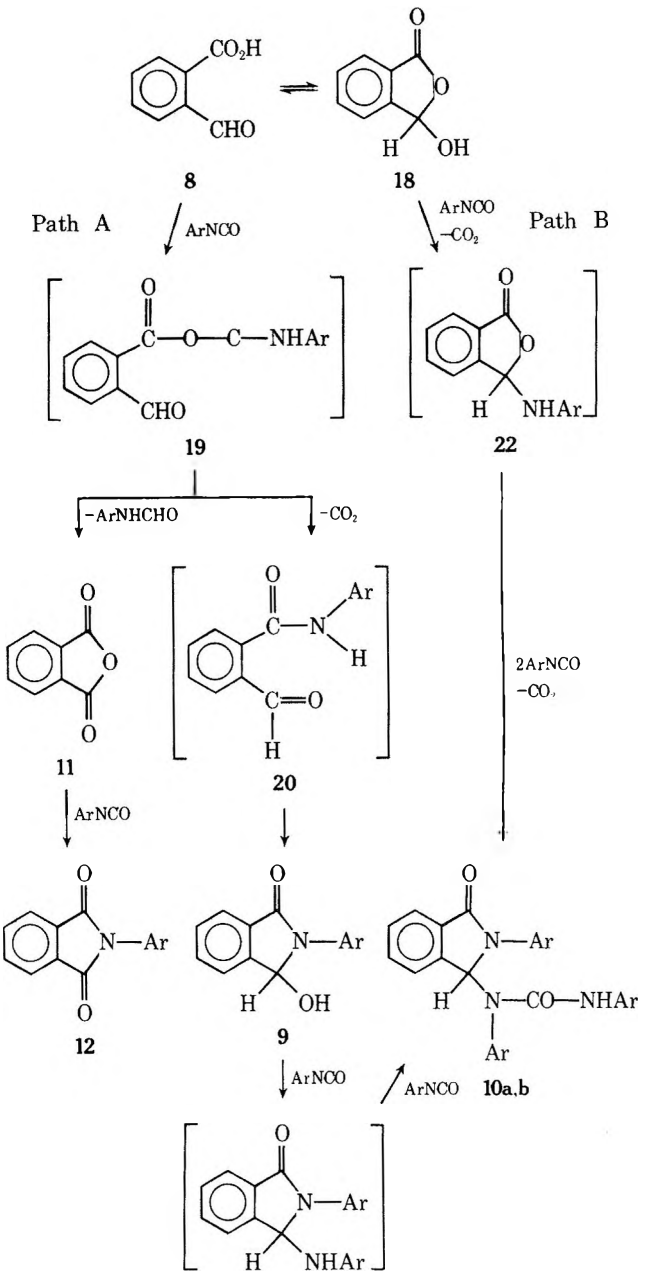


Chart V



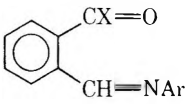
Although phenylisocyanate did not react with **23**, a fast reaction was observed with equimolar amounts of aniline (**4a**) and **23**, isolating the imine **24** and phthalimidine **21a** in 83 and 7% yields, respectively.

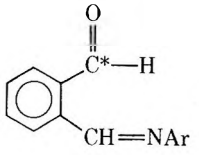
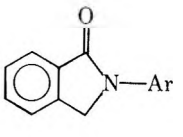
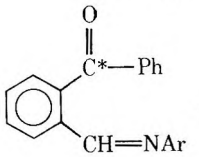
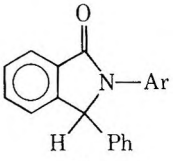
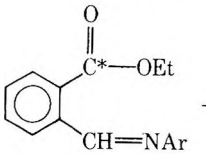
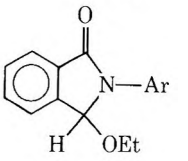
Pojer and his coworkers[6] obtained **21a** in their reaction of *"excess"* aniline with **23** but did not isolate **24**. They gave no discussion regarding the formation mechanism of **21a**.

On the other hand, Henderson and Dahlgren reported that aniline was not reactive toward **23** in dioxane at 21°.[7] Therefore we studied the reaction between **4a** and **23** in more detail. When the imine **24** was heated with aniline at 100° for 10 hr, **21a** was obtained in 64% yield. From this fact we could conclude that the formation of **21a** in the reaction between **23** and **4a** would involve the initial formation of **24**, followed by the nucleophilic attack of **4a** toward the CH=N bond.

A cyclization analogous to that involved in the formation of **21a** from **4a** and **24** was also observed when the imine **24** was heated with methanol or ethanol in the presence of sodium alkoxide to form **15a,b**. The reaction between **1a** and

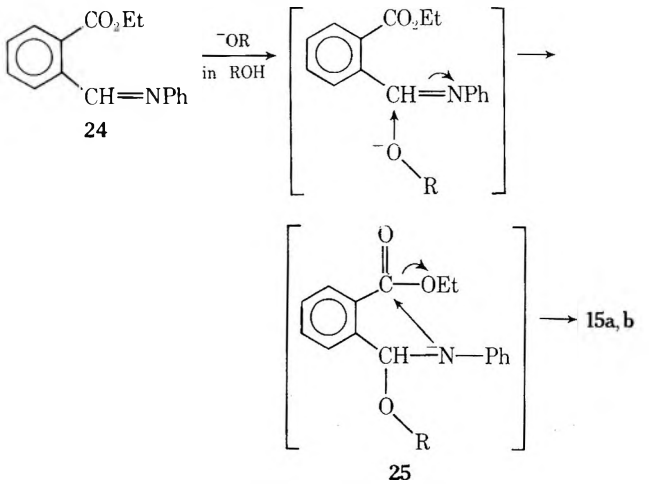
Table III
Cyclization of the Compounds of the Type



Reactant	Product	$\delta_{C=O}$
		190.7[a]
		194.8[b]
		164.9[c]

[a-c] The chemical shifts of carbonyl groups were approximated by those of (*a*) PhC*HO, (*b*) $Ph_2C^*=O$, (*c*) PhC^*O_2Et.

2a would imply the analogous isolation of **15b** from the thermolysis of **24**. Our attempt was, however, unsuccessful.



24

25

In summary, the cyclization of *o*-carbonylbenzylideneaniline seems to be initiated by the nucleophilic attack of nitrogen to carbonyl carbon; the electrophilicity of carbonyl carbon would make an important contribution. The electron density of carbonyl carbon affected by its environment is correlated with the chemical shift of C-13 nmr. As shown in Table III, the chemical shift of carbethoxy carbon is displayed at δ 164.9 ppm,[8a] but both aldehyde[8b] and ketone carbon[8c] are at lower fields than δ 190 ppm. These facts should support the above discussion. When the imine **24** was heated with the alkoxide ion, the nucleophilicity of imino nitrogen would increase by formation of intermediate **25**, resulting in a cyclization product.

Experimental Section[9]

Reaction of *o*-Benzoylbenzaldehyde (1a) with Aromatic Isocyanates 2a-d. General Procedure. A mixture of **1a** (4.0 g, 0.019 mol) and phenylisocyanate (**2a**) (2.5 g, 0.019 mol) was heated at 200° for 15 hr. The resulting dark brown cake was dissolved in benzene (10 ml), and chromatographed on neutral alumina (benzene was used as eluent) to afford 2,3-diphenylphthalimidine (**3a**) in 67% (3.6 g) yield, mp 192–194°; mass spectrum (70 eV) *m/e* 285 (M^+), 208 (M^+ − Ph), 180 (208 − CO). The spectral and analytical data are summarized in Table I.

Reaction of *o*-(*p*-Toluoyl)benzaldehyde (1b) with 2a. A Mixture of **1b** (2.2 g, 0.01 mol) and **2a** (1.2 g, 0.01 mol) was treated in a similar manner as the above. After similar work-up, the yield of **3e** was 1.5 g (52%), mp 190–190.5°.

Reaction of 1a with Aniline (4a). To a solution of **1a** (4.2 g, 0.01 mol) in benzene was added **4a** (1.9 g, 0.02 mol), and the resulting mixture was refluxed for 5 hr using a Dean-Stark trap. The solvent was evaporated *in vacuo* and the residue was chromatographed on alumina to give 3.7 g (65%) of **3a.**

Reaction of Phthalaldehydic Acid (8) with 2a. A mixture of **8** (4.5 g, 0.03 mol) and **2a** (3.07 g, 0.03 mol) in benzene (20 ml) was refluxed for 8 hr. The solvent was removed *in vacuo* and the resulting brown cake was chromatographed on neutral alumina using benzene, benzene–ethanol (99:1), and ethanol as eluents. The first fraction was concentrated and the residue was recrystallized from benzene–hexane to give a trace amount (0.01 g) of phthalic anhydride, mp 129–130 (lit.[10] 131.2°). Similar treatment of the second fraction afforded 1.0 g (15%) of *N*-phenylphthalimide (**12**), mp 208° (lit.[11] 208°). Similar treatment of the third fraction afforded 2.0 g (30%) of 3-hydroxy-2-phenylphthalimidine (**9**), mp 171.5–172.5° (lit.[12] 171–172°). The fourth fraction gave a trace amount of 3,3′-oxidiphthalide (**14**), mp 233–235° (lit.[13] 234–236°). The fifth fraction afforded 1.55 g (12%) of 3-(*N,N′*-diphenylureido)-2-phenylphthalimidine (**10a**), mp 203–203.5°: ir (Nujol) 3300 (NH), 1700 (C=O), 1670 (C=O) cm^{-1}; nmr (acetone-d_6) δ 6.37 (s, 1, CH), 6.48–7.8 (m, 9, aromatic protons), 8.8 (s, 1, NH); mass spectrum (70 eV) *m/e* 419 (M^+), 300, 299, 208.

Anal. Calcd for $C_{27}H_{21}O_2N_3$: C, 77.31; H, 5.05; N, 10.02. Found: C, 77.33; H, 5.08; N, 9.77.

The sixth fraction gave a trace amount (0.008 g) of *N,N′*-diphenylurea (**13**), mp 234–235°(lit.[14] 235°).

Reaction of 8 with *m*-Tolylisocyanate (2b). The reaction was carried out at the boiling temperature of benzene for 8 hr as described above using **8** (5.6 g, 0.037 mol) and **2b** (2.5 g, 0.042 mol). After similar work-up, the residue obtained was chromatographed on alumina using benzene–ethanol (98:2) to give 3-(*N,N′*-di-*m*-tolylureido)-2-*m*-tolylphthalimidine (**10b**) (4.5 g, 23%), which was the only product isolated, mp 166–168°: ir (Nujol) 3320 (NH), 1740 (C=O), 1640 (C=O) cm^{-1}; nmr (acetone-d_6) δ 2.1 (s, 3, CH_3), 6.0 (s, 1, CH), 6.2–7.9 (m, 16, aromatic protons), 8.05 (s, 1, NH).

Anal. Calcd for $C_{30}H_{27}O_2N_3$: C, 78.06; H, 5.83; N, 9.47. Found: C, 77.87; H, 5.90; N, 9.11.

Acid-Catalyzed Hydrolysis of 10a. A solution of **10a** (1.0 g, 0.0024 mol) in acetone (50 ml) was refluxed with concentrated hydrochloric acid (1.5 ml) for 3 hr. After removal of solvent, the residue was extracted with chloroform, washed with water, and dried over sodium sulfate. The chloroform layer was chromatographed on alumina to afford 0.25 g (47%) of **9**, 0.2 g (38%) of **13**, and 0.5 g (50% recovered) of **10a.**

Acid-Catalyzed Methanolysis of 10a. A solution of 1.0 g (0.0024 mol) of **10a** in 30 ml of aqueous methanol was refluxed with concentrated hydrochloric acid (1.0 ml) for 3 hr. The solvent was removed *in vacuo* and the residue was chromatographed on alumina to afford a trace of **9**, 0.5 g (87%) of 3-methoxy-2-phenylphthalimidine (**15a**), and 0.5 g (96%) of **13.**

15a had mp 79–80°: ir (Nujol) 1710 (C=O) cm^{-1}; nmr (CCl_4) δ 2.77 (s, 3, CH_3), 6.26 (s, 1, CH), 6.95–7.90 (m, 9, aromatic protons).

Anal. Calcd for $C_{15}H_{13}O_2N$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.25; H, 5.30; N, 6.05.

Acid-Catalyzed Ethanolysis of 10a. A solution of **10a** (2.0 g, 0.0048 mol) in 50 ml of 99% ethanol containing concentrated hydrochloric acid (1.0 ml) was refluxed for 3 hr. After similar work-up, the yield of **9** was 0.1 g (9%), that of **13** was 0.9 g (87%), and that of 3-ethoxy-2-phenylphthalimidine (**15b**) was 0.8 g (69%).

15b had mp 76–77°: ir (Nujol) 1710 cm^{-1}; nmr (CCl_4) δ 0.93 (t, 3, CH_3), 2.93 (m, 2, CH_2), 6.22 (s, 1, CH), 6.75–7.93 (m, 9, aromatic protons); mass spectrum (70 eV) *m/e* 253 (M^+), 224, 208, 180.

Anal. Calcd for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.78; H, 5.82; N, 5.66.

Reaction of 9 with 2a. A mixture of **9** (1.0 g, 0.0045 mol) and **2a** (1.1 g, 0.0093 mol) in benzene (20 ml) was refluxed for 6 hr. After removal of solvent, the residue was chromatographed on alumina to afford 0.5 g (27%) of **10a.**

Reaction of 3-Anilino-2-phenylphthalimidine (21a) with 2a. A mixture of **21a** (0.5 g, 0.0017 mol) and **2a** (0.5 g, 0.004 mol) was heated at 100° for 3 hr. Then the resulting mixture was chilled by ether, and filteration gave 0.6 g (86%) of **10a**.

Reaction of Ethylphthalaldehydate (23) with 4a. A mixture of **23** (5.34 g, 0.03 mol) and **4a** (2.8 g, 0.03 mol) in benzene (50 ml) was refluxed for 6 hr using a Dean-Stark trap. After removal of solvent, the residue was distilled under reduced pressure to afford 6.30 g (83%) of *o*-carbetoxybenzylideneaniline (**24**), bp 159° (2 mm): ir (Neat) 1720 (C=O), 1620 (C=N), 1260 ($-CO_2-$) cm^{-1}; nmr (CCl_4) δ 1.38 (t, 3, CH_3), 4.33 (q, 2, CH_2), 7.05–8.5 (m, 9, aromatic protons), 9.25 (s, 1, CH=N); mass spectrum (70 eV) *m/e* 253 (M^+), 224, 208, 280.

Anal. Calcd for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.94; H, 5.90; N, 5.59.

The residue after distillation was chromatographed on alumina to afford 0.63 g (7%) of **21a**, mp 160–161° (lit.[6] 162°).

Reaction of 24 with 4a. A mixture of **24** (3.0 g, 0.012 mol) and **4a** (1.12 g, 0.012 mol) was heated at 100° for 10 hr. Then the resulting mixture was chromatographed on alumina to afford 2.3 g (64%) of **21a**.

Reaction of 24 with *o*-Toluidine (4b). The reaction between **24** (3.0 g, 0.012 mol) and **4b** (1.29, 0.012 mol) was carried out in a similar manner as described for the reaction of **24** with **4a**. After similar work-up, the yield of 2-phenyl-3-(o-toluidino)phthalimidine (**21b**) was 3.75 g (*ca.* 100%), mp 167–168°: ir (Nujol) 3390 (NH), 1700 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.90 (s, 3, CH_3), 5.90–7.95 (m, 15).

Anal. Calcd for $C_{21}H_{18}ON_2$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.14; H, 5.62; N, 8.91.

Base-Catalyzed Methanolysis of 24. A solution of **24** ((3.00 g, 0.0012 mol) in absolute methanol was refluxed for 6 hr in the presence of sodium methoxide (0.3 g). After removal of solvent, the residue was extracted with ethylacetate, washed with water, and dried over sodium sulfate. The ethylacetate layer gave 2.35 g (82%) of **15a**.

Base-Catalyzed Ethanolysis of 24. A solution of **24** (3.0 g, 0.0012 mol) in ethanol was treated in the presence of sodium ethoxide (0.3 g) in a similar manner as the above. After similar work-up, the yield of **15b** was 1.70 g (56%).

Acknowledgment. We wish to thank Dr. K. Fujita and Dr. T. Hirose, JEOL Co, for C-13 nmr spectrum analysis.

Registry No.—**1a,** 16780-82-8; **1b,** 52920-19-1; **2a,** 103-71-9; **2b,** 621-29-4; **2c,** 86-84-0; **2d,** 2243-54-1; **3a,** 36149-34-5; **3b,** 53778-18-0; **3c,** 53779-19-1; **3d,** 53778-20-4; **3e,** 52920-23-7; **4a,** 62-53-3; **4b,** 621-29-4; **8,** 119-67-5; **9a,** 18167-15-2; **10a,** 52920-24-8; **10b,** 52920-27-1; **15a,** 52920-25-9; **15b,** 25770-48-3; **21a,** 19339-69-6; **21b,** 52920-26-0; **23,** 34046-43-0; **24,** 52920-28-2; 2-phenylphthalimidine, 5388-42-1.

Supplementary Material Available. Full carbon-13 nmr data for compounds 2-phenylphthalimidine, 2,3-diphenylphthalimidine, and 2-phenyl-2-(*p*-tolyl)phthalimidine will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the paters 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-74-3924.

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(3) See paragraph at end of paper regarding supplementary material.
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(9) Melting points are uncorrected. The infrared spectra were recorded on a JASCO-IR-E spectrometer. Nmr spectra were taken on JNM-C-60HL and JNM-PS/PFT-100 spectrometers; chemical shifts are expressed in parts per million (δ) down field from TMS as an internal standard. The mass spectra were obtained by HITACHI-RMU-6E spectrometer.
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Acylation of Amino Acid Schiff Bases

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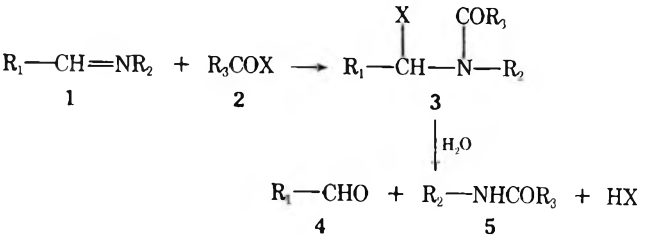
Acylating agents react with amino acid Schiff bases to form intermediates that can be hydrolyzed to acylated amino acids or dipeptides. This procedure offers a new method for preparing semisynthetic penicillins.

Previously, we had found it advantageous to isolate and purify 6-aminopenicillanic acid (6-APA), the basic intermediate for the production of semisynthetic penicillins, as its Schiff base.[1] We now wish to report that it is possible to acylate the Schiff base directly to form the desired penicillin derivative without the necessity of generating the free amino acid for use as the starting material.

It has long been known that the Schiff bases of amines (**1**) could readily be acylated with acid halides (**2**) or anhydrides.[2] The reaction involves an addition across the —CH=N bond to form a stable compound (**3**). Subsequent hydrolysis of the acid halide adduct yields the simple acylation product (**5**) of the original amine.



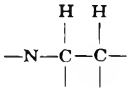
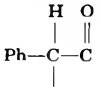
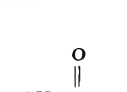
We have directed our studies toward the acylation of the Schiff bases of 6-APA salts and esters. The syntheses of penicillin V (**7a**) and its methyl ester (**7b**) were investi-

Table I
Nmr Data (ppm)[a]

Compd	Solvent	ArCH=N	PhCHCO	OCH_3	NHCH or $NHCH_2$ or $NHCH_3$	CH_2
10	$CDCl_3$	8.22	4.96	3.82	2.82 d (J_{NHCH_3} = 5.0)	
	C_6D_6	7.72	4.88	3.28	2.46 d (J_{NHCH_3} = 5.0)	
	CCl_4	8.11	4.83	3.78	2.80 d (J_{NHCH_3} = 5.0)	
14	$CDCl_3$	8.20	4.93	3.66	4.90 m	3.00
15	DMSO-d_6					
	NH_3^+ = 8.83 b		5.02 b	3.65	4.51 m	2.89
	NH = 9.12 d (J_{NHCH} = 8.0)					

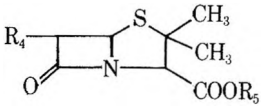
[a] b = broad; d = doublet; m = multiplet.

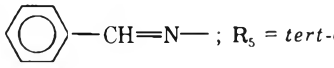
Table II
Nmr Spectrum of Intermediates[a]

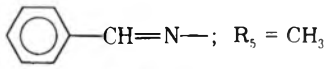
Compd	ArCH=N				CH_3O-	-CH_2	-CH_3
16	8.28	5.54 d (J = 4.0)				1.55	1.40
		5.63 q (J = 9.0, 4.0)	5.02	4.30		1.60	0.98
17	8.22	5.53 d (J = 4.0)				1.55	1.40
		5.63 q (J = 9.0, 4.0)	4.94	4.30	3.84	1.63	1.00

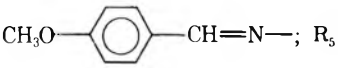
[a] Determined in $CDCl_3$.

gated, utilizing compounds **6a** and **6b** as substrates for the acylation studies.



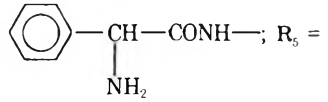
6a, R_4 =  ; R_5 = *tert*-octylamine salt

b, R_4 =  ; R_5 = CH_3

c, R_4 =  ; R_5 = *tert*-octylamine salt

7a, R_4 =  ; R_5 = H

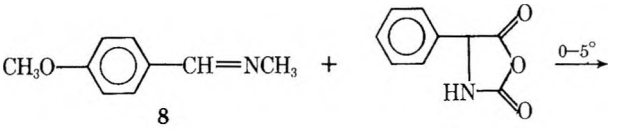
b, R_4 =  ; R_5 = CH_3

c, R_4 =  ; R_5 = H

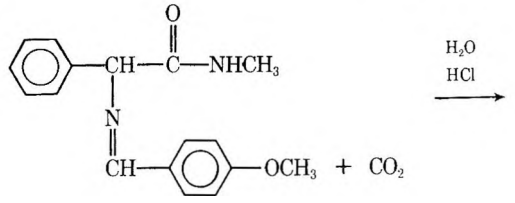
Upon fractional addition of phenoxyacetyl chloride to a cold solution of **6a** in $CDCl_3$, nmr and ir data showed the disappearance of the —CH=N double bond without the formation of an aldehyde. Free 6-APA was not formed in the reaction under anhydrous conditions, but was readily precipitated upon the addition of water to the reaction mixture. After the addition of approximately 1 equiv of acid chloride, the addition of a sodium 2-ethylhexanoate solution in anhydrous methyl isobutyl ketone did not produce the sodium salt of penicillin V. However, after hydrolysis of the intermediate with water, sodium penicillin V crystallized readily.

That the acid chloride did not form a mixed anhydride with the Schiff base carboxyl group that could act as the acylating agent for the 6-APA generated by the addition of water was demonstrated in the following manner: the methyl ester (**6b**) was treated with 1 equiv of phenoxyacetyl chloride in dry $CHCl_3$ at 0° for 35 min; after hydrolysis with dilute acid, an almost quantitative yield of penicillin V methyl ester (**7b**) was obtained. When the reaction was conducted in dry $CDCl_3$ and monitored by nmr, the imine proton absorption at δ 8.55 disappeared, apparently shifted upfield into the complex aromatic region, and no aldehyde proton absorption appeared at a lower field. Other acid chlorides (α-chlorophenacetyl, α-azidophenacetyl) reacted similarly.

However, ampicillin (**7c**) could not be isolated from the reaction of D-phenylglycyl chloride hydrochloride with the Schiff bases. Therefore, to prepare penicillins of this type by use of this principle, other reactions were considered. *N*-Carboxy-D-phenylglycine anhydride (NCA) has been used to prepare **7c** from 6-APA.[3] This reagent reacted with *p*-*N*-anisylidenemethylamine (**8**) in the following manner.



8 **9**



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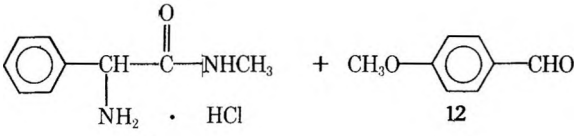
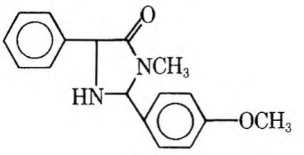


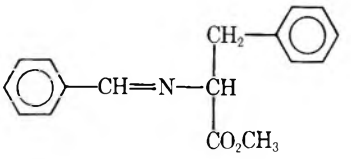
11 **12**



10a

The reaction was usually conducted at about 0–10° in $CDCl_3$ and followed spectrophotometrically in an nmr tube. The nmr data (Table I) (various solvents) indicated the formation of product **10**, and there was no evidence for the existence of the theoretical intermediate **10a**. Products **10** and **11** (*via* hydrolysis of **10**) were isolated and their structures were confirmed by elemental analysis.

NCA (**9**) reacted with the benzylidene Schiff base of L-phenylalanine methyl ester (**13**) to give the Schiff base of the dipeptide (**14**) in good yield. Hydrolysis of **14** afforded the amino acid derivative (**15**).



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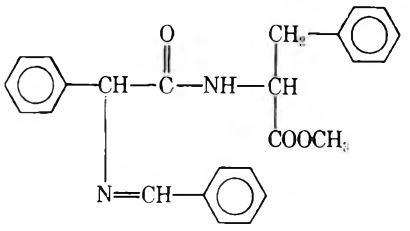
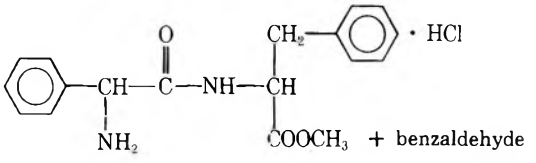


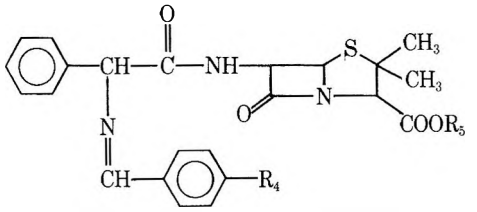
14

H_2O, HCl



15

The benzylidene (**6a**) and anisylidene (**6c**) Schiff base salts of 6-APA were found to react similarly with NCA, giving an intermediate Schiff base that could be hydrolyzed to ampicillin (**7c**). The structures of the intermediates (**16** and **17**) were assigned on the basis of nmr data for the reactants and the intermediates (Table II).



16, R_4 = H; R_5 = *tert*-octylamine salt

17, R_4 = OCH_3; R_5 = *tert*-octylamine salt

Thus, these procedures offer a general method for preparing semisynthetic penicillins from an intermediate Schiff base of 6-APA.[4] The reaction of NCA with the Schiff bases of amino acids may be useful in decreasing the polymeric reactions that often occur with this type of acylating reagent.[5]

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Nmr spectra were obtained by means of a Varian Associates A-60 spectrometer, using tetramethylsilane as the internal standard, and the data were reported as δ units. Mass spectra were determined on a MS-902 spectrometer.

Penicillin V (7a). A stirred slurry of **6a** (2.0 g, 4.6 mmol) in $CDCl_3$ (26 ml) was treated dropwise at 0–3° with a solution of phenoxyacetyl chloride (0.35 ml) in $CDCl_3$ (2 ml) over a period of 5 min. After an additional 7 min of reaction at 1–3°, the solution was sampled for ir and nmr assays (see text). A second portion of phenoxyacetyl chloride (0.35 ml in 2 ml of $CDCl_3$) was added and sampled again after 5 min. The ir curve of this material, when compared with the first spectrum, showed the disappearance of the —CH=N bond at 1640 cm^{-1}; there was no aldehyde present (ir and nmr). When a portion of the reaction solution (5 ml) was treated with 1.0 *N* sodium ethylhexanoate solution in methyl isobutyl ketone (1 ml), no precipitation occurred during a 4-hr period. When the cold reaction solution (10 ml) was agitated with D_2O (5 ml), an nmr spectrum of the organic phase showed an aldehyde peak. THE $CDCl_3$ layer was then mixed with 1.0 *N* sodium ethylhexanoate solution (2 ml) and, after 1.5 hr, sodium penicillin V (500 mg) was collected by filtration. Acidification afforded **7a**, identical with an authentic sample (ir and nmr).

Penicillin V, Methyl Ester (7b). A solution of **6b**[6] (510 mg, 1.5 mmol) in dry $CHCl_3$ (10 ml) was cooled to 0° and treated with phenoxyacetyl chloride (257 mg, 1.5 mmol) with stirring. A sample taken for ir indicated the disappearance of the imine band at 1640 cm^{-1}. After 35 min, the reaction mixture was poured into 0.1 *N* HCl (50 ml) and extracted with EtOAc (75 ml). The organic layer was washed twice with H_2O (50 ml) and with saturated NaCl solution (50 ml), dried ($MgSO_4$), and evaporated to dryness *in vacuo* to give **7b** (528 mg oil, 92% yield, ir identical with that of an authentic sample).

Reaction of *N*-Anisylidene Methylamine (8) with NCA (9). A stirred solution of **8**[7] (3.4 g, 23 mmol) in CH_2Cl_2 (100 ml) was cooled to 1–3° and treated, portionwise, with **9** (4 g, 23 mmol) over a 1-hr period. After 5.5 hr at that temperature, the mixture was treated with benzene (100 ml) and the CH_2Cl_2 was removed *in vacuo*. The benzene solution was lyophilized to give a semicrystalline solid (**10**, 6.9 g) that was washed with hexane and crystallized from ether to afford the analytical sample: mp 93°; mass spectrum M^+ 282 (calcd 282.3).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.44; N, 9.92. Found: C, 72.55; H, 6.54; N, 10.02.

The Schiff base appeared stable to water but, with dilute HCl in acetone, could be hydrolyzed to **11**, mp 239–240°.

Anal. Calcd for $C_9H_{13}ClN_2O$: C, 53.86; H, 6.54; N, 13.96; Cl, 17.66. Found: C, 53.90; H, 6.49; N, 13.77; Cl, 17.96.

***N*-Benzylidene Phenylalanine, Methyl Ester (13).** A stirred solution of L-phenylalanine methyl ester·HCl (8.6 g, 40 mmol) in H_2O (100 ml) was treated with a 40% NaOH solution to adjust the pH to 7.5. The solution was then treated with benzaldehyde (5.2 ml, 51 mmol) and the pH was maintained with NaOH at 6.5–7.0 for 3 hr. The oil that separated initially during the reaction crystallized and was collected by filtration to give **13** (8.8 g). Recrystallization of **13** from hexane gave the analytical sample, mp 52–53°.

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.31; H, 6.42; N, 5.24. Found: C, 76.54; H, 6.40; N, 5.22.

Schiff bases of amino acids have been difficult to isolate because of the equilibrium formed during their preparation.[8] Direct isolation from H_2O, rather than from organic solvents, is made possible by the insolubility of **13**.

Phenylglycylphenylalanine, Methyl Ester Hydrochloride (15). A stirred solution of **13** (5 g, 18.7 mmol) in CH_2Cl_2 (125 ml) was treated at 0–3° with **9** (3.6 g, 20.3 mmol) over a 20-min period. The mixture was stirred at 1–3° overnight, filtered, and then treated with H_2O (30 ml). The CH_2Cl_2 was removed *in vacuo* and the resulting gummy precipitate crystallized on standing. The solid was collected by filtration and washed with hexane to give **14** (mp 80–82°).

Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.97; H, 6.05; N, 7.00. Found: C, 74.03; H, 5.97; N, 7.29.

Hydrolysis of **14** (1.0 g) was carried out at pH 1.0 in a mixture of CH_2Cl_2 (10 ml) and H_2O (2 ml). The crude salt (**15**, 0.5 g) was collected by filtration and crystallized from *i*-PrOH to give the analytical sample, mp 218°.

Anal. Calcd for $C_{18}H_{21}ClN_2O_3$: C, 61.97; H, 6.08; N, 8.03; Cl, 10.16. Found: C, 61.75; H, 6.11; N, 7.87; Cl, 10.11.

Ampicillin (7c). A stirred slurry of **6c** (5 g, 10.8 mmol) in CH_2Cl_2 (50 ml) was cooled to 1–3° and treated with CF_3CO_2H (0.4 ml, 5.3 mmol), followed by the portionwise addition of **9** (2.1 g, 11.8 mmol) over a 20-min period. After 2 hr at this temperature, the mixture was treated with H_2O (50 ml) and agitated at pH 5.0–5.2 for 3 min. The Schiff base (**16**) could be isolated (3.3 g) from the

aqueous phase by neutralizing the solution with *tert*-octylamine to pH 7.5 and adding benzaldehyde (0.7 ml).

Anal. Calcd for $C_{31}H_{42}N_4O_4S$: S, 5.65; N, 9.9. Found: S, 5.36; N, 9.7.

The Schiff base **16** (3.2 g) was washed with toluene (5 ml) and dissolved in a mixture of H_2O (7 ml) and methyl isobutyl ketone (7 ml), then the pH was adjusted to 1.5 with HCl. The pH was adjusted once more to 4.9 with NaOH, and the precipitate was collected by filtration and air dried to afford **7c** (950 mg, as its trihydrate). The ir and nmr spectra were identical with those of an authentic sample.

Acknowledgment. The authors thank Mrs. B. Toeplitz for the ir spectra, Dr. P. Funke for the mass spectra, and Mr. J. Alicino and his staff for microanalyses.

Registry No.—**6a**, 53059-76-0; **6b**, 37628-54-9; **6c**, 53059-78-2; **7a**, 87-08-1; **7b**, 20109-75-5; **7c**, 69-53-4; **8**, 13114-23-3; **9**, 3412-73-5; **10**, 53059-79-3; **11**, 53059-80-6; **13**, 40216-77-1; **14**, 53128-97-5; **15**, 53059-81-7; **16**, 53129-37-6; **17**, 53176-74-2; phenoxyacetyl chloride, 701-99-5; L-phenylalanine methyl ester hydrochloride, 7524-50-7; benzaldehyde, 100-52-7.

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(7) "Organic Synthesis," Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 605 (*N*-benzylideneemethylamine).
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The Stieglitz Rearrangement with Lead Tetraacetate and Triarylmethylamines

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The results of the lead tetraacetate induced Stieglitz rearrangement with various mono-*para*-substituted triarylmethylamines are presented. Migratory aptitudes have been determined. In addition the results of trapping experiments are also given. A concerted mechanism is postulated consistent with all the data.

A common feature of the Curtius–Hofmann–Lossen and the lead tetraacetate-induced rearrangement of carboxylic acid amides is the migration of a group to a potentially electron-deficient nitrogen to yield an isocyanate (eq 1).[1]

$$R{-}\underset{\underset{O}{\|}}{C}{-}\ddot{N}{-}Y \longrightarrow O{=}C{=}\ddot{N}{-}R + :Y \qquad (1)$$

$$Y = N_2,\ Cl^-,\ {}^-O_2CR,\ Pb(OAc)_2$$

The four rearrangements differ in their departing groups. The similarity to the Stieglitz rearrangement and its variations[2] with N-substituted amines is striking (eq 2). A re-

$$R_3C{-}\ddot{N}{-}Y \longrightarrow R_2C{=}\ddot{N}{-}R + Y: \qquad (2)$$

$$Y = N_2,\ Cl^-,\ O{=}PCl_3$$

cent preliminary paper[3] extended the likeness when a lead tetraacetate induced Stieglitz rearrangement was reported on triphenylmethylamine (eq 2, Y = $Pb(OAc)_2$) (eq 3).

$$Ph_3CNH_2 \xrightarrow[\Delta]{LTA,\ C_6H_6} PhN{=}CPh_2 + HOAc + Pb(OAc)_2 \qquad (3)$$

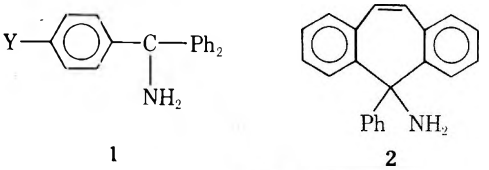
(85–90%)

On the basis of trapping experiments, electronic properties of the migrating group and kinetic isotope effects a concerted mechanism is strongly indicated[4] for the former rearrangements (eq 1). With respect to the Stieglitz rearrangements the situation is less clear. Migratory aptitudes spanning a range of 9 for the *p*-anisyl group to 0.4 for the *p*-nitrophenyl group argued in favor of a concerted pathway for the phosphorus pentachloride induced rearrangement of mono-para-substituted trityl-*N*-hydroxylamines.[5] Solely as a result of the statistical distribution of products obtained from phenyl and *p*-halophenyl migration in the base-induced Stieglitz rearrangement with *p*-halotrityl-*N*-haloamines, and the lack of rearrangement of *N*-methyl-*N*-chlorotritylamine, Stieglitz proposed a nitrene intermediate. Abramovitch[6] offers evidence that the thermolysis of tertiary alkyl azides gives rise to a singlet nitrene and their photochemical decomposition does not involve nitrenes.[7] Both conclusions are in opposition to those of Saunders.[8]

This paper attempts to elucidate the intermediate in the lead tetraacetate induced Stieglitz rearrangement from the results of migratory aptitude studies and trapping experiments.

Results

The mono-para-substituted triphenylmethylamines **1a–c** were prepared from the corresponding alcohols by converting them to the azides followed by lithium aluminum hydride ($LiAlH_4$) reduction. The amines **1d** and **1e** were synthesized by ammonolysis of the corresponding halides. The amine **2** was prepared from the alcohol by conversion to the azide followed by reduction with $LiAlH_4$.



1 **2**

a, Y = H; **b**, Y = Cl; **c**, Y = CH_3; **d**, Y = OCH_3; **e**, Y = NO_2

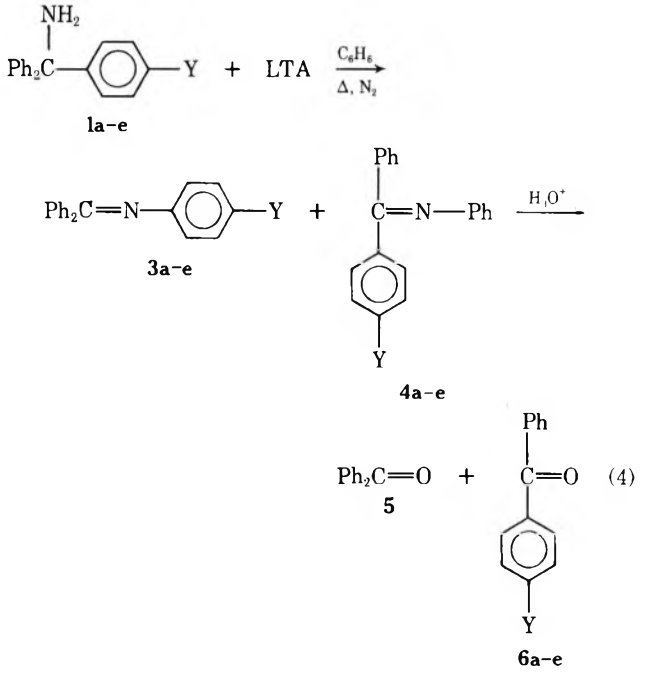
Treatment of the amines **1a–e** with acetic acid free lead tetraacetate (LTA) in refluxing benzene under nitrogen led to a rapid consumption of LTA (15–20 min as monitored by starch–iodide test paper). The product mixture in each case was obtained in close to quantitative yield (90–95%).

Table I
Reaction of LTA with Triarylmethylamines (Eq 4)

Amine 1	Overall % yield[a]	Relative % yield[b] 3	4	MA
a H	90	a 100		1.0[c]
b *p*-Cl	95[e]	b 38.6	41.4	1.86
c *p*-CH_3	92	c 84.4	15.6	10.9
d *p*-OCH_3	93	d 98.7	1.3	152[d]
e *p*-NO_2	92	e 16.3	83.7	0.39

[a] Average crude yields of product isolated after removal of solvent *via* rotary evaporator followed by vacuum pump; duplicate determinations. [b] Triplicate determination by glpc using biphenyl as internal standard. [c] Migratory aptitude (MA) = 2(% benzophenone)/% *p*-Y-benzophenone; phenyl taken as relative standard with migratory aptitude set equal to one by definition. [d] The migratory aptitude calculated should be viewed as the minimum value for the *p*-anisyl group (see ref 32). [e] Approximately a 10% yield of what is believed to be the acetamide of amine **1b** was also isolated.

Infrared and nmr spectroscopy indicated that they were essentially mixtures of isomeric imines (eq 4). Separation of

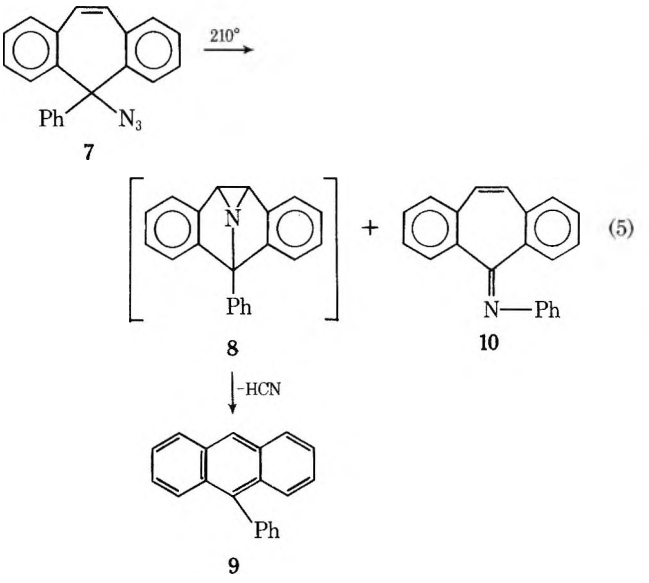


the isomeric imines by column chromatography has been reported to be fruitless.[8] Quantitative analysis was therefore performed indirectly by glpc procedures on the corresponding benzophenones (**5** and **6a-e**) derived from the acid hydrolyses of the isomeric imine mixtures.[9]

Based upon the product distributions observed and the statistical preference factor of 2 for the phenyl migration *vs.* the para-substituted phenyl, migratory aptitudes were calculated. The results are presented in Table I.

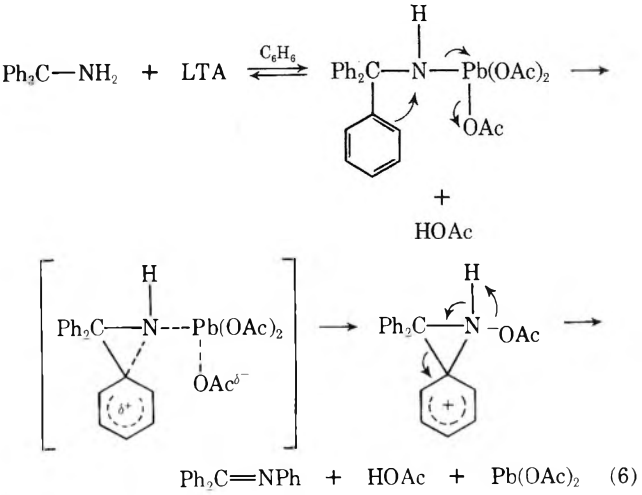
The LTA-induced rearrangement of triphenylmethylamine was also conducted in cyclohexene–benzene[3] and in pure cyclohexene in an attempt to trap a possible nitrene intermediate. However, no decrease in yield of benzophenone anil (**3a**) was noted nor was any spectral evidence[10] obtained which would indicate the presence of an aziridine. The only other expected material present was identified as 3-acetoxycyclohexene from its boiling point and ir spectrum.

Looker[11] has recently succeeded in trapping a possible nitrene (eq 5) with a suitably disposed double bond in **7**. Accordingly, **2** was treated with LTA in benzene and the *only* product isolated was **10** (85%).



Discussion

Bartlett[12] has observed that one of the best criteria for the operation of a cationic mechanism in 1,2-rearrangements should be the experimental finding of relative migratory aptitudes similar to those characteristic of the Wagner–Meerwein, pinacol, and related rearrangements and different from those prevailing in reactions of a known free radical type. Such a distinction should be readily made as it is generally well known that the migratory aptitudes observed in free radical migrations have been considerably less selective electronically[13] than those observed in the corresponding cationic migrations. More recently, the use of aromatic migratory aptitudes in order to determine the nature of the migrating terminus has been extended to include 1,2 shifts from carbon to oxygen[12,14,15] and nitrogen[5,8,16] as well as from carbon to carbon. The values of the migratory aptitudes accumulated (spanning *p*-anisyl, 152, to *p*-nitrophenyl, 0.39) (Table I) argue against either a free radical mechanism or a nitrene[8] mechanism. Rather the pathway involving a concerted migration of the aryl group with the departure of the lead acetate or its triacetoxyplumbate anion precursor seems most consistent with the data (eq 6). The results, however, do not preclude a nitrenium ion rationale from consideration; however, arguments[17] have been presented that a nitrenium ion should be of considerably higher energy than its carbonium ion analog owing to the higher electronegativity of nitrogen. Thus, a greater driving force should exist for a rearrange-



ment to be synchronous in systems which could also potentially proceed *via* a nitrenium ion.

Since migratory aptitudes indirectly reflect rates of phenyl *vs.* para-substituted phenyl migration, a modified Hammett equation can be employed to analyze such data (eq 7). Such a quantitative treatment has been employed

$$\log MA = \rho\sigma^{+} \qquad MA \propto 2k_{p-Y}/k_{H} \qquad (7)$$

by McEwen[17] and more recently by Starnes.[18] A plot our data employing the modified Hammett equation gave a good straight line whose slope, ρ, was -1.70 ($r = -0.903$, $s = 0.54$, $n = 5$). The result is consistent with a transition state in which a partial positive charge is generated in the migrating aryl group (eq 6). Analogous linear plots were obtained using the data of Saunders[8,16] (triarylmethyl azides, pyrolytic and photolytic decompositions) and Newman[5] (triarylmethylhydroxylamines with phosphorus pentachloride) yielding ρ values of -0.63, -0.036, and -0.89, respectively. One tentative conclusion which may be drawn is that in the several variations of the Stieglitz rearrangement it cannot be strictly said that there is one mechanism operative. More accurately, there are several mechanisms involving a spectrum of transition states differing in the degree of aryl participation invoked by the departure of the particular leaving group. The formation of a discrete nitrene intermediate could be said to constitute a limiting case.

The chief difficulty inherent in a successful intermolecular trap of an alkyl nitrene has been attributed to their extremely brief lifetime[19] and relatively high reactivity.[20] Therefore the negative intermolecular trapping results cannot be viewed as further evidence against a nitrene (and indirectly favoring the concerted mechanism) but must be viewed as inconclusive. However, greater success[11,21] has been reported in trapping alkyl nitrenes on an intramolecular basis. Thus, the reported[11] successful intramolecular trapping of the alkyl nitrene derived from 7 (eq 5) becomes significant with respect to the present study in that the negative[22] trapping result from the reaction of LTA with 2 lends indirect support for the concerted mechanism.

Experimental Section[23,24]

Triphenylmethylamine (1a). Method A. Into a dry three-necked round-bottom flask equipped with a reflux condenser, addition funnel, drying tubes, and magnetic stirrer were placed 2.0 g (0.052 mol) of $LiAlH_4$ and 100 ml of anhydrous ether. A solution of 10 g (0.035 mol) of triphenylmethyl azide[8] in 50 ml of ether was slowly added dropwise. The mixture was refluxed for 2 hr and decomposed.[25] The mixture was filtered and washed with ether, and the combined ether extracts were dried ($MgSO_4$). The solvent was distilled off and the residual solid was recrystallized from absolute ethanol, yielding 7.7 g (85%) of a white solid: mp 97–100° (lit.[26] mp 99–100°); ir 3300, 3370 cm^{-1} (NH_2); nmr τ 2.75 (s, 15 H, phenyl), 7.75 (s, 2 H, NH_2).

Method B. The procedure of Vosburgh[27] was followed employing a 250 ml benzene solution of trityl chloride (5.6 g, 0.02 mol) and soda-lime-dried NH_3 gas. The solid was recrystallized from absolute ethanol to yield 2.3 g (44%) of a white solid, mp 97–100°, identical in all properties with the material prepared by method A.

***p*-Chlorophenyldiphenylmethylamine (1b)** was prepared according to method A using 9.5 g (0.030 mol) of azide,[8] 4.0 g (0.104 mol) of $LiAlH_4$, and 175 ml of ether. There was obtained 8.2 g (0.028 mol) (94%) of amine **1b** as a colorless viscous gum:[27] ir (neat) 3370, 3305 cm^{-1} (NH_2); nmr τ 2.6–3.2 (m, 14 H, aromatic), 7.75 (broad s, 2 H, NH_2).

The acetamide of amine **1b** was prepared and recrystallized from benzene–cyclohexane: mp 205–208°; ir (KBr) 3260, 1660 cm^{-1}.

Anal. Calcd for $C_{21}H_{18}NOCl$: C, 75.11; H, 5.40; N, 4.17. Found: C, 74.95; H, 5.67; N, 4.30.

Diphenyl-*p*-tolylmethylamine (1c) was prepared according to method A employing 9 g (0.030 mol) of azide,[8] 2.0 g of $LiAlH_4$, and 175 ml of ether. Recrystallization (EtOH) yielded 6.9 g (0.025 mol) (83%) of **1c** as a white solid: mp 74.5–76°; ir (KBr) 3310, 3380 cm^{-1} ($-NH_2$); nmr ($CDCl_3$) τ 2.7 (s, 10 H, phenyl), 2.86 (s, 4 H, *p*-tolyl), 7.67 (s, 3 H, CH_3), and 7.88 (s, 2 H, NH_2).

Anal. Calcd for $C_{20}H_{19}N$: C, 87.89; H, 7.01; N, 5.12. Found: C, 87.73; H, 7.01; N, 5.22.

***p*-Anisyldiphenylmethylamine (1d)** was prepared according to method B using 6.08 g (0.020 mol) of chloride[28] in 250 ml of benzene. The crude amine was chromatographed on neutral alumina (80–200 mesh). Elution with benzene and 50% ether–benzene afforded 5.3 g (0.018 mol) (91%) of **1d** as a colorless, viscous gum: ir (neat) 3300, 3370 cm^{-1} ($-NH_2$); nmr τ 2.55–3.45 (m, 14 H, aromatic), 6.4 (s, 3 H, OCH_3), 7.95 (broad s, 2 H, NH_2).

Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.99; H, 6.42; N, 4.84.

The acetamide of amine **1d** was prepared and recrystallized from 50% aqueous ethanol and then cyclohexane: mp 178–180°; ir (KBr) 3270, 1660 cm^{-1}.

Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.56; H, 6.56; N, 4.32.

Diphenyl-*p*-nitrophenylmethylamine (1e) was prepared according to method B using 10 g (0.027 mol) of bromide[8,18] in 250 ml of benzene. The initially obtained gum was dissolved in hot CCl_4 and allowed to stand overnight at $-10°$. The resulting solid was recrystallized (EtOH) to yield 4.25 g (0.014 mol, 51%) of a white solid: mp 118–120°; ir (KBr) 3315, 3375 cm^{-1} (NH_2); nmr τ 1.85–2.6 (4 H, A_2B_2, J = 8.3 Hz, *p*-nitrophenyl), 2.78 (s, 14 H, phenyl), 7.85 (broad s, 2 H, $-NH_2$).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.97; H, 5.30; N, 9.20. Found: C, 75.01; H, 5.21; N, 9.31.

5-Amino-5-phenyl-5*H*-dibenzo[*a*,*d*]cycloheptene (2) was prepared according to method A using 7 g (0.023 mol) of the azide[11] and 2.2 g (0.058 mol) of $LiAlH_4$ in 200 ml of ether. Several recrystallizations from ethene–ligroin (bp 60–90°) afforded 4.8 g (0.017 mol) (73%) of **2**: mp 170–171.5°; ir (KBr) 3305, 3370 cm^{-1} ($-NH_2$); nmr τ 1.8–2.0 (m, 2 H, aromatic), 2.3–2.9 (m, 9 H, aromatic), 3.2–3.7 (m, 4 H, 2 vinyl, 2 aromatic), 7.9 (s, 2 H, NH_2).

Anal. Calcd for $C_{21}H_{17}N$: C, 88.99; H, 6.06; N, 4.94. Found: C, 89.02; H, 6.02; N, 4.89.

Reaction of LTA with Triphenylmethylamine (1a). Into a dry, three-necked, round-bottom flask equipped with a dropping funnel, reflux condenser, and magnetic stirrer was placed 4.9 g (0.01 mol) of LTA (under nitrogen). The flask was covered with aluminum foil and then evacuated on a vacuum pump (1 torr) for 2 hr after which 100 ml benzene was added. A solution of 2.6 g (0.01 mol) of **1a** in 100 ml of benzene was added dropwise, after which the reaction mixture was refluxed for 1 hr. The solution was cooled to room temperature, filtered, and washed successively with 10 ml of ethylene glycol, 10 ml of water, 25 ml of 10% Na_2CO_3 solution, and 10 ml of water. After drying ($MgSO_4$) the solvent was removed (rotary evaporator) and the residue recrystallized (EtOH) to yield 2.2 g (0.0085 mol) (85%) of **3a**: mp 111–113° (lit.[29] mp 113–114°); ir and nmr spectra of this material were superimposable on those derived from authentic[29] **3a**.

In a subsequent run the LTA was refluxed in benzene solution with 2 g of anhydrous $CaCO_3$ for 1 hr before admitting the solution of **1a**. The product isolated, 2.35 g (0.009 mol) (90%), **3a** was identical with that previously obtained.

In a third experiment, the reactants were refluxed for 1 hr in cyclohexene. There was isolated 2.66 g of crude material: ir 1740, 1240 ($OCOCH_3$), and 1620 cm^{-1} (C=N). A comparison of the relative intensities of these absorption bands with those derived from authentic mixtures of **3a** and 3-acetoxycyclohexene[30] of known composition allowed the ester's relative composition to be estimated at 15%. Recrystallizations (EtOH) yielded 2.25 g (0.0087 mol, 87%) of **3a**. From the filtrate there was obtained 3-acetoxycyclohexene, bp 71–72° (17 torr) [lit.[30] bp 68–71° (12 torr)].

Control Acid Hydrolysis of 3a. Into a 50-ml flask was placed 1.02 g (3.9 mmol) of **3a**, followed by 10 ml of glacial acetic acid, 30 drops of water, and 30 drops of concentrated hydrochloric acid. The mixture was kept at room temperature for 49 hr. Distilled water (10 ml) and 0.6 g (3.9 mmol) of biphenyl were added before extraction with ether. The ether solution was dried (Na_2SO_4), concentrated, and subjected to glpc analysis.[24a] Two peaks were observed corresponding to biphenyl and benzophenone (**5**), respectively. The area of each peak was determined.[24] The methods[24] gave relative yields of **5** of 98.6 and 93.8%. The peak for **5** was also collected: ir 1667 cm^{-1}.

Reaction of LTA with 1c. The reaction was carried out as de-

scribed for **1a** employing 4.9 g (0.01 mol) of LTA and 2.73 g (0.01 mol) of **1c**. There was obtained 2.48 g (0.0092 mol, 92%) of a yellow-orange oil: ir (neat) 1620 cm^{-1} (C=N–); nmr τ 2.25–3.7 (m, 14 H, phenyl), 7.9 (s, 3 H, CH_3). The oil was subjected to the acid hydrolysis as described for **3a**, and the ether extract was analyzed by glpc[24a] (242°). The observed peaks corresponded to biphenyl, benzophenone (**5**), and *p*-methylbenzophenone (**6c**). The identity of each peak was confirmed by selective peak enhancement upon coinjection with the authentic material. The peaks were suitable for area measurement.[24] The value for the migratory aptitude for the *p*-tolyl group is given in Table I.

Reaction of LTA with 1d. The reaction was conducted as described for **1a** and **1c** with 4.9 g (0.01 mol) of LTA and 2.89 g (0.01 mol) of **1d**. Following the work-up, 2.63 g (0.0093 mol, 93%) of a yellow-orange oil was obtained: ir (neat) 1610 cm^{-1} (C=N–); nmr τ 2.6–3.5 (m, 14 H, aromatic), 6.3 (s, 3 H, OCH_3).

A portion of the oil was dissolved in hot ethanol and allowed to stand overnight at −10°. A yellow solid, **3d**, was isolated, mp 68–70° (lit.[31] mp 71°). Structure **3d** was also confirmed on the basis of the acid hydrolysis (below).

The remainder of the oil was hydrolyzed, the ether extract from which was analyzed by glpc.[24a] In addition to the biphenyl and benzophenone peaks, a very small peak corresponding to that of *p*-methoxybenzophenone (**6d**) was noted. The identity of this peak was confirmed by selective peak enhancement upon coinjection with authentic **6d**. The relative corrected areas[24] of these peaks were used in order to calculate the value for the migratory aptitude for the *p*-anisyl group[32] (Table I).

The aqueous acidic fraction of the hydrolysate was neutralized and extracted with ether. The ether was dried (Na_2SO_4), and evaporation of the ether left an oil which crystallized when cooled. Recrystallization (water) yielded only *p*-anisidine, mp 50–54° (lit.[33] mp 57°). The ir was superimposable upon that of an authentic sample.

Reaction of LTA with 1e. The same procedure was followed using 1.38 g (4.6 mmol) of **1e** and 2.44 g (5 mmol) of LTA. Following the work-up 1.3 g (4.2 mmol, 92%) of a yellow-orange oil was isolated. The major component of the oil **4e** was isolated by crystallization (EtOH): mp 125–127°; ir 1625 (C=N–), 1520, 1352 cm^{-1} (NO_2).

Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.49; H, 4.67; N, 9.27. Found: C, 75.26; H, 4.62; N, 9.31.

A 200-mg sample of **4e** was hydrolyzed by refluxing for 2 hr in 50 ml of 10% hydrochloric acid. The solution was extracted with benzene, the extracts were dried ($MgSO_4$), and the solvent was largely removed (rotary evaporator). Analysis by glpc procedures[24b] revealed a single peak corresponding to that of *p*-nitrobenzophenone (**6e**).

In a subsequent experiment the initial oil was subjected to acid hydrolysis (the extracting solvent was benzene). The concentrated benzene solution was analyzed by glpc procedures.[24b] Three peaks corresponding to biphenyl, benzophenone, and *p*-nitrobenzophenone (**6e**) were observed. The corrected relative areas[24] were used in order to calculate a value for the migratory aptitude of the *p*-nitrophenyl group (Table I).

Reaction of LTA with 1b was carried out with 2.93 g (0.01 mol) of **1b** and 4.9 g (0.01 mol) of LTA. After work-up there was obtained 2.74 g (0.0095 mol, 95%) of a yellow-orange oil: ir (film) 3450 (–NH), 1665 (C=O), 1618 cm^{-1} (C=N–); nmr τ 2.3–3.6 (m, 14 H, aromatic). Assuming the extraneous component to be the acetamide of **1b**, the relative abundance of the acetamide was estimated at 10% by comparison of the relative intensities of the carbonyl and imino ir absorption peaks of the oil with those of prepared mixtures with known compositions. Acid hydrolysis of the oil and glpc analysis were then performed.[24b] Peaks corresponding to biphenyl, benzophenone, and *p*-chlorobenzophenone (**6b**) were observed. The corrected relative areas measured[24] were used in order to obtain a value of the migratory aptitude for the *p*-chlorophenyl group (Table I).

Reaction of LTA with 2 was studied employing 2.83 g (0.01 mol) of **2** and 4.9 g (0.01 mol) of LTA as before except that the effluent gases from the reaction vessel passed through a gas-washing bottle containing 75 ml of distilled water to which four drops of 50% sodium hydroxide had been added. After the usual work-up, 75% of the benzene was removed and tlc plates were spotted with microspots of the reaction mixture, authentic **10**, and **9**. These plates were developed with 50% v/v benzene–ligroin (bp 60–90°) and then examined first under uv lamp (Burton Model 1910) and then after treatment in an iodine chamber. No fluorescent spot corresponding to **9** was observed, only one corresponding to **10**. An aliquot of the reaction mixture was also analyzed by glpc procedures[24c] with coinjected biphenyl. Peaks attributed to biphenyl and **10** were only observed. The remainder of the benzene was removed yielding an oil which when triturated with ligroin (bp 63–75°) crystallized. Two recrystallizations (methylcyclohexane) gave 2.4 g (0.0085 mol, 85%) of **10**: mp 122–124° (lit.[11] mp 122–123°); ir 1620 cm^{-1} (C=N–); nmr τ 1.8–2.0 (m, 2 H, aromatic), 2.3–2.9 (m, 9 H, aromatic), and 3.2–3.7 (m, 4 H, aromatic and vinyl). Acid hydrolysis of **10** (500 mg) for 1 hr (reflux) with 50 ml of 10% hydrochloric acid yielded after work-up and recrystallization (MeOH), 350 mg (95%) of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, mp 86–88° (lit.[34] mp 89°); ir 1645 cm^{-1}.

The aqueous trap gave a negative test for cyanide ion.[35]

In another run the reaction mixture was chromatographed directly on 60 g of Florisil (Baker 60–80 mesh) employing the technique of Loev.[23] Elution with 50% (v/v) *n*-hexane–benzene (800 ml) and benzene (1000 ml) gave 2.12 g (0.0075 mol, 75%) of **10**, mp 122–124°.

Registry No.—**1a**, 5824-40-8; **1b**, 53060-10-9; **1b** acetamide, 53060-11-0; **1c**, 53060-12-1; **1d**, 53060-13-2; **1d** acetamide, 53060-14-3; **1e**, 53060-15-4; **2**, 53060-16-5; **3a**, 574-45-8; **3b**, 17273-16-4; **3c**, 24215-01-8; **3d**, 42834-19-5; **4b**, 53060-17-6; **4e**, 53060-18-7; **5**, 119-61-9; **10**, 27971-66-0; LTA, 546-67-8; triphenylmethyl azide, 14309-25-2; *p*-chlorophenyldiphenylmethyl azide, 13189-73-6; diphenyl-*p*-tolymethyl azide, 13189-72-5; 5-phenyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl azide, 27915-27-1.

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Since the reaction of LTA with ketonic Schiff bases (**3** and **4**) has received little attention, product stability was demonstrated when no change was observed when **3** and **4** were refluxed 0.5 hr in benzene containing a 50% excess of LTA.
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(22) Since the pyrolysis of **7** was performed at 210°, the possibility arose that the initially formed azasemibullvalene **8** might have decomposed at that elevated temperature (producing **9**) and yet been stable in the refluxing benzene used in our experiments. Accordingly, several aliquots of a concentrated benzene solution of the reaction products were injected directly onto a gas chromatograph whose injection port, column, and detector temperatures were all thermostated above 210°. No peak corresponding to 9-phenylanthracene (**9**) was detected.
(23) Melting points were determined on a Thomas-Hoover Unimelt apparatus. Infrared spectra were run as 20% solutions in CCl_4 unless otherwise specified. Nmr spectra were determined as 10% solutions in CCl_4 unless otherwise specified. Ultraviolet spectra were recorded on a Cary 14 spectrophotometer. Column chromatography was carried out using the dry column method of B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967). Analytical thin-layer chromatography was carried

out employing Eastman Kodak precoated silica gel chromatogram sheets. The benzene used in the LTA reactions was Baker spectrograde, dried over sodium and redistilled prior to use. All aryl halides used were freshly distilled prior to use. Lead tetraacetate, 10% moist with acetic acid, was obtained from Arapahoe. All other reagents were of the highest purity commercially available. All LTA reactions were run under nitrogen.

(24) Gas chromatographic analyses were performed on an F&M Scientific Model 720 dual column temperature programmed gas chromatograph. Quantitative analysis of the reaction products in a given mixture was performed by internal standardization method with relative percentages being assessed *via* cutting and weighing or triangulation methods. These methods generally gave answers within 5% of one another. The columns employed were as follows. (a) Column A: 4 ft × 0.25 in Apiezon L on Chromosorb P (60–80 mesh); 40 psi of He (60 ml/min); 230–245°; temperature programmed to 280° in order to elute *p*-methoxybenzophenone with minimum tailing. (b) Column B: 2 ft × 0.25 in. 19% Silicone gum rubber (UC-bw98) on Chromosorb P (60–90 mesh); 40 psi of He (60 ml/min); 200°. (c) Column C: 4 ft × 0.25 in. 20% Silicone gum rubber (SE-30) on Chromosorb W; 40 psi of He (60 ml/min); 210°.

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Notes

Trifluoroacetic Acid as a Medium for Aromatic Nitration Using Sodium Nitrate

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The nitration of aromatic systems is one of the most thoroughly studied of all organic reactions, and the central role of the nitronium ion, NO_2^+, in these processes has been well established.[2] Trifluoroacetic acid (TFA) has occasionally been used as a medium for electrophilic aromatic substitutions[3] and, in particular, Brown and Wirkkala used neat TFA and anhydrous nitric acid to nitrate benzene and toluene.[4] Some of our work on the use of TFA as a medium for the permanganate oxidation of hydrocarbons[5] involved cryoscopic measurements in TFA and these results indicated that nitronium and nitrosonium ions could be conveniently generated in TFA using sodium nitrate and sodium nitrite, respectively. We report herein the results obtained for nitration of benzene, toluene, and phenol, using these reagents.

The data presented in Table I show that nitration is almost quantitative after 4 hr of reaction with sodium nitrate. The mixture of isomers resulting from the nitration of toluene is similar to that reported by Brown and Wirkkala (ortho, meta, para = 61.6%, 2.6%, 35.8%).[4]

Trace amounts of phenolic substances were detected in the reaction products.[6] Such products may result either from oxygen attack by the ambident nitronium ion, followed by solvolysis and rapid nitration to produce nitrophenols, or by an addition–elimination mechanism[7] to give phenyl trifluoroacetate which then undergoes solvolysis and nitration.[8]

Attempts to use this medium for nitrosations were unsuccessful, as the data in Table I illustrate, even though cryoscopic and spectroscopic measurements indicated that up to 50% of the nitrite salt was converted to nitrosonium ion. Complex formation between nitrosonium ion and the arene was observed, as had been previously reported.[9] The small amount of nitration that occurs under these conditions is presumably the result of disproportionation[10] or oxidation[11] of nitrogen(III).

Table I

Reactants	Products	% yield[a]	% Conversion[b]
Benzene and $NaNO_3$	Nitrobenzene	99.9	100
	Phenolic products[c]	~0.05	
Toluene and $NaNO_3$	*p*-Nitrotoluene[d]	30.0	95
	o-Nitrotoluene	63.7	
	m-Nitrotoluene	1.2	
Phenol and $NaNO_3$	Tar[c]		
Benzene and $NaNO_2$	Nitrobenzene	3	3
Toluene and $NaNO_2$	Nitrotoluene mixture	~2	~2

[a] Based on quantities of starting materials used. [b] Based on quantities of starting materials consumed. [c] Indicated by the reversible changes in spectra of the product mixture produced by acidification and basification: λ_{max} 415, 366 nm in base and 320 nm (sh) in acid; a 1:1 mixture of o- and *p*-nitrophenols has λ_{max} at 415 nm in base and 330 nm in acid. [d] The mixture of nitrotoluenes was analyzed by vpc on a 10% silicon GS-SF-96 firebrick 60/80, 0.25-in. × 10-ft column at 162° and with 40 cm³/min of helium; it was then matched against known samples. Retention times were as follows: *o*-nitrotoluene, 8.5 min; *p*-nitrotoluene, 11.1 min., *m*-nitrotoluene, 10.5 min; toluene, 1.5 min. [e] Rapid, exothermic reaction occurred; could be hazardous.

Experimental Section

In a typical experiment 0.01 mol of sodium nitrate or sodium nitrite was added to 25 ml of neat TFA and then 0.01 mol of the arene was added while the mixture was stirred magnetically. The reaction was allowed to continue for 4 hr at room temperature, after which it was quenched by the addition of 20 ml water and by the addition of enough sodium hydroxide (either as 6 *M* solution or as pellets) to achieve a pH ≥10. The resulting solution was saturated with sodium chloride and successively extracted with three 50-ml portions of ether. The ether extracts were combined and dried over anhydrous magnesium sulfate and then reduced to 50 ml by flash evaporation. The concentrates were weighed and analyzed by vpc.

If TFA recovery is important, the sodium chloride saturation step can be omitted; then, after the ether extraction, the aqueous

solution is slowly acidified by the addition of concentrated sulfuric acid until 5 parts per volume of aqueous solution have been added. This mixture is distilled to remove TFA, which will distil along with some water. The fraction between 71 and 105° is collected, treated again with sulfuric acid, and redistilled. Anhydrous TFA results; bp 71.2°.

All compounds used were of reagent grade. The arenes were purified by distillation or recrystallization; the TFA was distilled prior to use.

Registry No.—TFA, 76-05-1; $NaNO_3$, 7631-99-4; $NaNO_2$, 7632-00-0; toluene, 108-88-3; phenol, 108-95-2; benzene, 71-43-2.

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Study of the Trifluoroethanolysis of Cyclobutylcarbinyl and Related *p*-Bromobenzenesulfonates

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Our previous investigation[2] of the solvolytic behavior of cyclobutylcarbinyl brosylate (4-OBs) and related compounds revealed the kinetic and product distribution data were accommodated by Scheme I where solvent capture of a carbon-bridged species accounts for at least 99% of the acetolysis product. Justification for the intermediacy of a carbon-bridged species was based upon (1) the presence of 99% ring-expanded product, (2) the absence of a significant 1-ring substituent effect upon solvolytic reactivity, (3) the absence of cyclopentene product, and (4) the establishment of a good correlation between log k_t for 4-OBs and log k_t for neophyl tosylate.

Prompted by these findings, we extended our investigation to include a product distribution study in 2,2,2-trifluoroethanol (TFE) of the following cycloalkylcarbinyl brosylates. This paper reports the analysis of the product distribution data according to Scheme I in an effort to gain insight into the role of the solvent in the product partitioning process.

$(CH_2)_nCHCH_2OBs$

$n + 1 = 4$, 4-OBs
$n + 1 = 5$, 5-OBs
$n + 1 = 6$, 6-OBs

The product data are summarized in Table I. The vapor-phase chromatographic separations and characterizations of products were carried out on a Carbowax 20M–silver nitrate column. Urea was used as a buffer and product studies were conducted at the same temperature as the kinetic investigations.[2] Previously reported[3] stability studies have established that the reported products are indeed the initially formed products and not those of subsequent reactions.

On the basis[2] that solvolysis occurs by one or more of the discrete pathways outlined in Scheme I, the data in Table II are readily obtained. It is interesting to note that the solvent change from acetic acid to TFE is characteried by a decrease in the per cent k_s reaction product for all three substrates, most dramatically for 6-OBs, which confirms the unique ability of TFE to accentuate neighboring group participation under nonacidic conditions.[3d,4–6] This result is readily accommodated by the interesting solvent properties of TFE,[7–10] particularly its enhanced ionizing ability relative to acetic acid without any significant change in solvent nucleophilicity,[10,11] for a substantial body of information[12–14] has accumulated in support of increasing anchimeric assistance (relative to solvent assistance) with increasing ionizing strength of the solvent in solvolysis reactions.

Focusing our attention on the product data summarized in Table I, we observe that the change from acetic acid to TFE results in a considerable increase in the amount of ring-expanded olefin obtained from the solvolysis of 4-OBs and 5-OBs. Thus the trifluoroethanolysis of 4-OBs yields

Scheme I

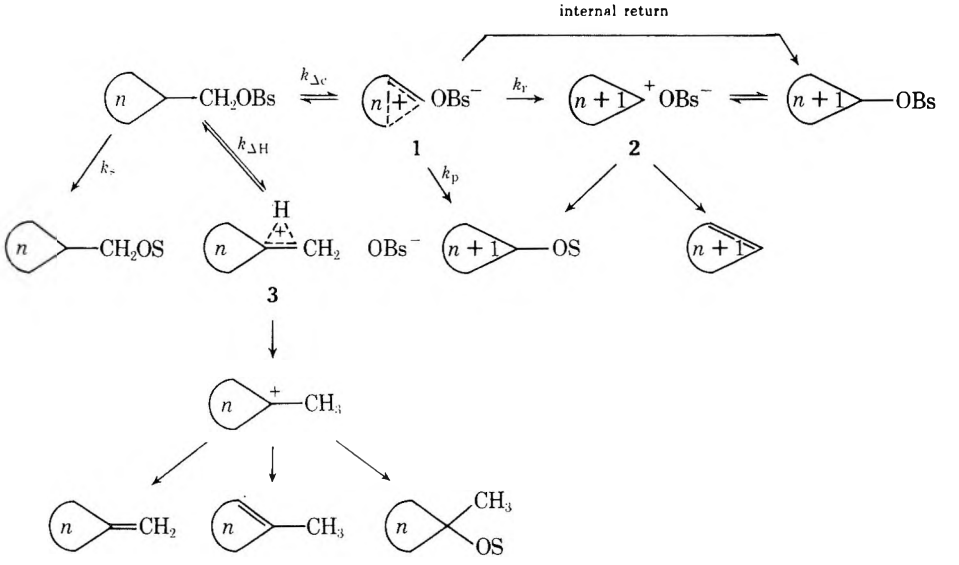
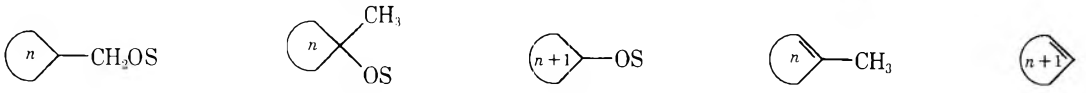


Table I
Per Cent Product Data for Investigated Substrates[a,b]



Substrate	Solvent	A	B	C	D	E
4-OBs	AcOH[c]	1		99		
	CF_3CH_2OH			50		50
c-C_5H_9OBs	AcOH[c]			80		20
	CF_3CH_2OH[d]			24		76
5-OBs	AcOH[c]	4	3	91	1	1
	CF_3CH_2OH			34		66
c-C_6H_{11}OTs	AcOH[e]			15		85
	CF_3CH_2OH			20		80
6-OBs	AcOH[c]	47	13[f]		40[f]	
	CF_3CH_2OH	8	56		12[g]	

[a] Acetolysis at 75°; 2,2,2-trifluoroethanolysis at 55°. [b] In acetolysis, OS = OAc, and in trifluoroethanolysis, OS = OCH_2CF_3. [c] Taken from ref 2. [d] Taken from ref 3f; 97% trifluoroethanol–3% water. [e] Taken from data of J. D. Roberts and V. C. Chambers, *J. Amer. Chem. Soc.*, **73**, 5034 (1951). [f] Under reaction conditions, there is some conversion of 1-methylcyclohexyl acetate to 1-methylcyclohexene. [g] Also 24% methylenecyclohexane.

Table II
Partitioning of Solvolysis Reactions According to Scheme I

Substrate	Solvent	% k_s	% $k_{\Delta H}$	% $k_{\Delta c}$
4-OBs	AcOH[a]	1	0	99
	CF_3CH_2OH[b]	0	0	100
5-OBs	AcOH[a]	4	5	91
	CF_3CH_2OH[b]	0	66	34
6-OBs	AcOH[a]	47	53	0
	CF_3CH_2OH[b]	8	92	0

[a] Data taken from ref 2 at 75°. [b] Data taken from ref 2 at 55°.

50% cyclopentene while no detectable olefin was found in the acetolysis run. Similarly, the trifluoroethanolysis of 5-OBs yields 66% cyclohexene while only 2% olefin (1% *via* $k_{\Delta H}$ pathway) was found in the acetolysis run.

In view of Bartlett's suggestion[3b] that the folded geometry of bridged intermediate **1** is unfavorable for olefin production and our corroborating observation[2] of the absence of olefin among the ring-expanded acetolysis products of 4-OBs and 5-OBs, the detection of appreciable quantities of cycloalkenes in the trifluoroethanolysis products of 4-OBs and 5-OBs is mechanistically significant. We propose that in contrast to the nearly exclusive $k_{\Delta c}^1$ pathway ($k_{\Delta c}$ followed by k_p) postulated for acetolysis,[2] the $k_{\Delta c}^2$ pathway ($k_{\Delta c}$ followed by k_r) competes with the $k_{\Delta c}^1$ pathway in the trifluoroethanolysis reactions. That is, part of the product results from solvent interaction with the carbon-bridged species **1** and part results from solvent interaction with the classical cation **2**.[15]

It can be estimated, on the basis that all cyclopentene product is from **2** and the *E/S* ratio observed for the trifluoroethanolysis of cyclopentyl brosylate[3e] accurately represents the product partitioning from **2**, that 34% of 4-OBs suffers trifluoroethanolysis by $k_{\Delta c}^1$ and 66% by $k_{\Delta c}^2$ pathways. Likewise it can be estimated that 17% of 5-OBs suffers trifluoroethanolysis by $k_{\Delta c}^1$ and 83% by $k_{\Delta c}^2$ pathways.

This solvent-induced change in reaction pathway is understandable in terms of the following considerations. First, Winstein, *et al.*,[17] have supplied considerable evidence for the involvement of at least three different types of carbonium ion intermediates (the intimate (or tight) ion pair, the solvent-separated ion pair, and the dissociated ion) in solvolysis reactions and they have also supplied evidence that the solvent may enter the picture as a nucleophile (or base) at any of the several stages of reaction intermediates as depicted in Scheme II. Second, there is some

Scheme II

$$RX \rightleftharpoons R^+X^- \rightleftharpoons R^+\|X^- \rightleftharpoons R^+ + X^-$$

product set 1 product set 2 product set 3

evidence for the involvement of a later stage carbonium ion intermediate in the trifluoroethanolysis product step than that involved in the acetolysis product step. For instance, Shiner[18] has argued from α-secondary deuterium isotope effects on reactivity of benzyl halides in solvolysis reactions that the products are mostly derived from the solvent-separated ion pair in TFE instead of the intimate ion pair as in acetic acid. And third, in accord with generally accepted theory, the high ionizing strength[19] and low nucleophilicity[10] of TFE should lead to greater structural reorganization of the carbonium ion than in acetic acid before the product step. In summary, then, we propose solvolysis of 4-OBs or 5-OBs in TFE generates a looser ion pair than in acetic acid and that with such a looser ion pair k_r is competitive with k_p.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Hitachi Perkin-Elmer R-24 instrument with tetramethylsilane as internal standard. A Beckman GC-4 chromatographic instrument equipped with a thermal conductivity detector, a Disc automatic integrator-printer, and a 24 ft × 0.25 in. column of 20% Carbowax 20M 2% $AgNO_3$ on Chromosorb W, AW-DMCS (45–60 mesh), was used for analytical gc work.

Cyclobutylcarbinyl (4-OBs), cyclopentylcarbinyl (5-OBs), and cyclohexylcarbinyl (6-OBs) brosylate were the same materials as previously described.[2]

Cyclopentyl brosylate was prepared, by published procedure,[2] in 35% yield: mp (after two recrystallizations from 12:1 petroleum ether (bp 30–60°)–ethyl acetate) 45–46° (lit.[20] mp 45.8–46.6°).

Cyclohexyl *p*-toluenesulfonate was prepared, by published procedure,[21] in 75% yield: mp (after two recrystallizations from petroleum ether (bp 30–60°), 44.3–44.9° (lit.[22] mp 44.4–44.8°).

Preparation of Reference Olefins. Cyclopentene, cyclohexene, cycloheptene, 1-methylcyclohexene, and methylenecyclohexane were purchased from Aldrich Chemical Co. and used as received. 1-Methylcyclopentene was the same material as previously described.[2]

Solvent. 2,2,2-Trifluoroethanol (Aldrich Chemical Co.) was redistilled prior to use and analytical purity checked by gc and nmr.

Product Studies. A. Cyclobutylcarbinyl Brosylate (4-OBs). Cyclobutylcarbinyl brosylate (5 mmol) was dissolved in sufficient solvent (containing 7.5 mmol of urea) to give 25 ml of solution. Five-milliliter aliquots were transferred to 10 ml ampoules, sealed under N_2 and immersed in a constant temperature bath at 55°. After 10 half-lives, the ampoule contents were poured into 50 ml of water and the resultant mixture was extracted once with a 5-ml portion of methylene chloride. The extract was washed four times with 10-ml portions of cold water and dried over magnesium sulfate. The crude extract on analysis by gas chromatography (50°, 50 ml/min He flow rate) gave rise to two peaks, A (2.2 min retention time) and B (6.3 min retention time), with 1:1 relative peak areas, in addition to the air and solvent peaks. Peak A was identified as cyclopentene by comparison of retention time with that of an authentic sample. Peak B was identified as cyclopentyl 2,2,2-trifluoroethyl ether by nmr analysis: δ 3.70 (q, 2 H, OCH_2CF_3)[3d,10,16] and 1.5–2.0 (broad 8 H, ring protons).

B. Cyclopentylcarbinyl Brosylate (5-OBs). Cyclopentylcarbinyl brosylate was solvolyzed as in section A. After 10 half-lives, the ampoule contents were poured into 50 ml of water and the resultant mixture was extracted three times with 25-ml portions of methylene chloride. The combined extracts were washed three times with 30-ml portions of cold water and dried over anhydrous sodium sulfate, and most of the solvent was removed by distillation with a Nester-Faust NFA-200 autoannular still. The residue on analysis by gas chromatography (60°, 40 ml/min He flow rate) gave rise to two peaks, A (2.5 min retention time) and B (7.8 min retention time), with 1.9:1.0 relative peak areas, in addition to the air and solvent peaks. Peak A was identified as cyclohexene by comparison of retention time with that of an authentic sample. Peak B was identified by nmr analysis as cyclohexyl 2,2,2-trifluoroethyl ether: δ 3.73 (q, 2 H, OCH_2CF_3)[3d,10,16] and 3.2–3.5 (broad, 1 H, $C_2CHOCH_2CF_3$).[3d]

C. Cyclohexylcarbinyl Brosylate (6-OBs). Cyclohexylcarbinyl brosylate was solvolyzed and worked up as in section B. The residue on analysis by gas chromatography (60°, 40 ml/min He flow rate) gave rise to four peaks, A (3.0 min retention time), B (3.3 min retention time), C (9.3 min retention time), and D (12.4 min retention time), with 2.8:1.4:6.6:1.0 relative peak areas, in addition to the air and solvent peaks. Peaks A and B were identified as methylenecyclohexane and 1-methylcyclohexene respectively by comparison of retention times with those of authentic samples. Peak C was isolated by preparative gas chromatography and identified by nmr analysis as 1-methylcyclohexyl 2,2,2-trifluoroethyl ether: δ 3.70 (q, 2 H, OCH_2CF_3)[3d,10,16] and 1.1 (s, 3 H, CCH_3). Peak D was identified as cyclohexylmethyl 2,2,2-trifluoroethyl ether on the basis of retention time and nmr analysis of peak C fraction.

D. Cyclohexyl Tosylate. Cyclohexyl tosylate was solvolyzed as in section B. The solvolysis solution was then injected into the gas chromatograph, giving two peaks, A and B, with 4.0:1.0 relative peak areas, in addition to a very large solvent peak. By comparison with the chromatograms obtained in section B, A and B were identified as cyclohexene and cyclohexyl 2,2,2-trifluoroethyl ether, respectively.

Registry No.—4-OBs, 51108-24-8; 5-OBs, 38806-24-5; 6-OBs, 51108-25-9; c-$C_6H_{11}OTs$, 953-91-3.

References and Notes

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(15) The $k_{\Delta c}{}^3$ pathway,[2] internal return isomerization to a cycloalkyl brosylate, is considered unlikely for two reasons: (1) there is no evidence[2] for the $k_{\Delta c}{}^3$ pathway in the acetolysis of either 4-OBs or 5-OBs, and (2) internal return isomerization in TFE has been observed to be no greater[5] or less[16] than that in acetolysis.
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Mobile Keto Allyl Systems. XVI.[1] The Thermal Decomposition of 2-(α-*N*-Methyl-*tert*-butylaminobenzyl)-1-indenone A Deamination–Rearrangement

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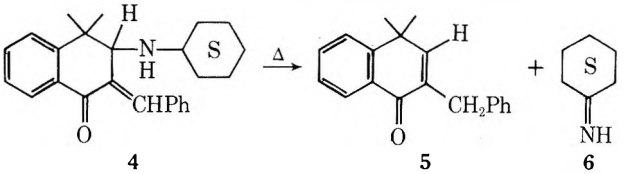
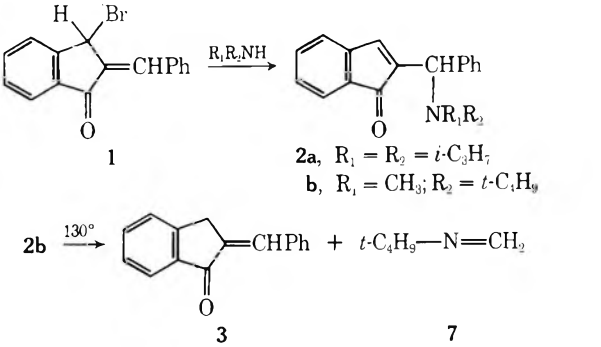
The first reported thermal decomposition of a β-keto allyl amine resulting in a deamination–rearrangement was that by Maury and Cromwell[2] in which 2-(α-diisopropylaminobenzyl)-1-indenone (**2a**) was found to form 2-benzal-1-indanone (**3**) upon heating and what was tentatively identified by vpc as diisopropylamine. Since that initial report Glaros and Cromwell[3,4] have studied extensively the thermal decomposition of the related β-keto allyl amine **4** and have shown that the decomposition proceeds *via* a retroene mechanism producing α,β-unsaturated ketone **5** and presumably imine **6**. In view of these previous results a rein-



4 **5** **6**

vestigation of the thermal rearrangment of compounds related to **2a** was undertaken. The results of this study for 2-(α-*N*-methyl-*tert*-butylaminobenzyl)-1-indenone (**2b**) are the subject of the present paper.

When **2b**, prepared by the reaction of *N*-methyl-*tert*-butylamine with 3-bromo-2-benzal-1-indanone[5] (**1**), was heated in a sealed tube at 130° for 3 hr 2-benzal-1-indanone (**3**) was isolated in 85% yield. In addition evidence was obtained for the existence of *N*-methylene-*tert*-butylamine (**7**) as a coproduct. Treatment of the decomposition



1 **2a**, $R_1 = R_2 = i\text{-}C_3H_7$; **b**, $R_1 = CH_3$; $R_2 = t\text{-}C_4H_9$

3 **7**

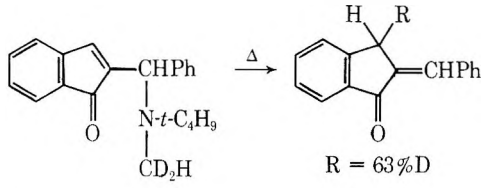
Table I
Kinetic Data for 2b and 4 in Isooctane

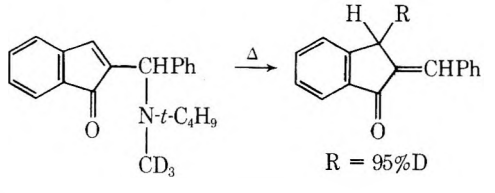
Temp, °C	K^a, sec^{-1} 2b	4
105	3.1×10^{-5} (± 0.1)[b]	
111	5.3×10^{-5} (± 0.4)	
120	1.2×10^{-4} (± 0.1)	2.3×10^{-5} (± 0.1)
130	2.7×10^{-4} (± 0.2)	
135		1.5×10^{-4} (± 0.1)
150		1.9×10^{-4} (± 0.4)
	E_a = 25.8 kcal	E_a = 25.4 kcal
	ΔS^+ = −13 eu at 135°	ΔS^+ = −17 eu at 135°

[a] Average of three runs at each temperature unless otherwise noted. [b] Average of two runs.

mixture with aqueous hydrogen chloride, followed by evaporation of the aqueous extract, afforded *tert*-butylamine hydrochloride in 30% yield, obviously resulting from the acid hydrolysis of imine **7**. Additional evidence to support the formation of **7** was provided by following the course of the decomposition in a sealed nmr tube. Two new absorptions appeared at δ 1.17 (d, J = 2 Hz) and 3.90 (d, J = 1.2 Hz), which increased in intensity with time at the expense of the absorptions of **2b** at δ 1.10 and 5.40. The new low-field absorption was assigned to the resonance for the benzal proton in **3** while the high-field adsorption was assigned to the resonance of the *tert*-butyl group in **7** based upon comparison with a pure sample. The methylene protons of **7**, although not readily discernible, were found by integration to lie under the aromatic multiplet.

The formation of α,β-unsaturated ketone **2** and imine **7** appears to be the result of a retroene reaction being operative. Additional proof of this hypothesis was found in a deuterium labeling experiment. Not only does a retroene reaction demand the formation of imine **7**, but also it requires that the hydrogen α to the nitrogen in the amino moiety be transferred to the benzylic position. Indeed when 2-(α-*N*-methyl-d_2-*tert*-butylaminobenzyl)-1-indenone and 2-(α-*N*-methyl-d_3-*tert*-butylaminobenzyl)-1-indenone were allowed to decompose in the usual manner an 63 and 95% deuterium transfer, respectively, to the 3 position was established.





Although an extensive kinetic investigation was not carried out, a comparison of the first-order kinetic results obtained with those of Glaros and Cromwell[4] for **4** shows a marked similarity (Table I). The difference in the entropies of activation we feel may be the result of a more crowded transition state for **4**. It is therefore believed that both **2b** and **4** decompose by a similar retroene reaction mechanism, one which may best be explained as "a concerted reaction passing through a dipolar transition state."[4]

Experimental[6] Section

Preparation of *N*-Methyl-*tert*-butylamine and Related Compounds. A. *N*-Methyl-*tert*-butylamine. The procedure of Heath and Mattocks[7] was employed with modification. To 22.0 g (0.579 mol) of lithium aluminum hydride suspended in 300 ml of dry ether was added 23.0 g (0.227 mol) of *N*-*tert*-butylformamide (Frinton Laboratories) over a 0.5-hr period. The mixture was refluxed for 2.5 hr and then allowed to stir overnight at room temperature. It was next cooled in an ice bath and the excess lithium aluminum hydride decomposed by the careful dropwise addition of water. The resulting aluminum salts were filtered and washed well with ether. The filtrate was dried over magnesium sulfate and distilled through a 10-cm Vigreux column. The fraction boiling at 50–70° was collected and redistilled to yield 5.0 g (24.8%) of *N*-methyl-*tert*-butylamine as a colorless liquid, bp 64–66° (lit.[8] bp 58–60°): nmr ($CDCl_3$) 2.33 (s, 3 H, $-CH_3$), 1.43 (bs, 1 H, NH), 1.10 (s, 9 H, *tert*-butyl). The forerun, bp 33–50°, was treated with dry HCl gas and gave 9.9 g (35.8%) of *N*-methyl-*tert*-butylamine hydrochloride as colorless plates, mp 254–256° (lit.[7] mp 252–254°).

B. *N*-Methyl-d_2-*tert*-butylamine. The same procedure as in (A) above was used and lithium aluminum deuteride was employed in lieu of lithium aluminum hydride. From 2.0 g (0.047 mol) of lithium aluminum deuteride and 4.0 g (0.039 mol) of *N*-*tert*-butylformamide, there was obtained 0.52 g (15.3%) of product, bp 65–66°: nmr ($CDCl_3$) δ 2.31 (m, 1 H CHD_2), 1.46 (bs, 1 H, NH), 1.10 (s, 9 H, *tert*-butyl); mass spectrum 97.4% d_2.

C. *N*-Methyl-*N*-nitroso-*tert*-butylamine. The procedure of Heath and Mattacks[7] was employed without variation. From 18.0 g (0.261 mol) of sodium nitrite and 12.0 g (0.098 mol) of *N*-methyl-*tert*-butylamine hydrochloride there was obtained 10.1 g (88.0%) of the *N*-nitroso amine as a lemon-yellow oil, bp 31–33° (0.2 mm) (lit.[7] bp 66° (5 mm)); nmr ($CDCl_3$) δ 3.00 (s, 3 H, CH_3), 1.53 (s, 9 H, *tert*-butyl).

D. *N*-Methyl-d_3-*N*-nitroso-*tert*-butylamine. To 2.0 g (0.017 mol) of *N*-methyl-*N*-nitroso-*tert*-butylamine was added 45 ml of 1.3 *M* sodium deuterioxide in deuterium oxide and 20 ml of methanol-d_1 (for solubility). The resulting mixture was heated under reflux for 18 hr. The reaction mixture was cooled and extracted with ether (4 × 50 ml). The ether extracts were dried and evaporated to yield 1.9 g of a yellow oil: nmr ($CDCl_3$) δ 3.00 (m, <1 H, CD_3), 1.53 (s, 9 H, *tert*-butyl); mass spectrum 82.8% d_3.

Recycling of the above product with fresh sodium deuterioxide solution and proceding as above gave 1.7 g (85.0%) of a yellow oil: mass spectrum 94.8% d_3.

E. *N*-Methyl-d_3-*tert*-butylamine Hydrochloride. Into a solution of the above trideuterated nitroso amine (1.7 g, 0.014 mol) in 35 ml of dry ether was passed dry HCl gas until a permanent dark yellow color resulted. The reaction mixture was then stirred at room temperature for 1 hr. It was then filtered and the precipitate washed well with dry ether and air dried. Recrystallization from ethanol gave 1.0 g (55.6% of the amine hydrochloride salt), mp 254–256°: nmr ($CDCl_3$). δ 1.42 (s); mass spectrum 94.8% d_3.

F. *N*-Methylene-*tert*-butylamine (7). The procedure of Hurwitz[9] was utilized without variation. From 13.0 g (1.40 mol) of *tert*-butylamine and 125 ml (1.60 mol) of 37% formaldehyde solution there was obtained 79.8 g (66.9%) of the Schiff base as a colorless liquid, bp 64–66° (lit.[9] bp 63–65°): nmr ($CDCl_3$) δ 7.37 (d, J = 2 Hz, 2 H, $N{=}CH_2$), 1.17 (d, J = 2 Hz, 9 H, *tert*-butyl).

Preparation of 2-(α-Aminobenzyl)-1-indenones. The preparation of several aminoindenones has already been described in the literature.[10] The same general procedure was employed to prepare the following indenones.

A. 2-(α-*N*-Methyl-*tert*-butylaminobenzyl)-1-indenone (2b). From 0.50 g (0.0017 mol) of 3-bromo-2-benzal-1-indanone and 0.29 g (0.0033 mol) of *N*-methyl-*tert*-butylamine was obtained 0.40 g (77.2%) of **2b** as orange crystals, mp 66–67°; ir (CCl_4) 1715 cm^{-1} (C=O); uv (hexane) λ_{max} (ϵ) 240 (30,000), 307 (1800), 317 (1600), 333 (1040), 390 (800), 407 (1000), 430 nm (1,200); nmr ($CDCl_3$) δ 7.63–6.85 (m, 10 H, 9 aromatic protons + 1 vinyl proton), 5.42 (d, J = 0.8 Hz, benzylic), 2.26 (s, 3 H, $-CH_3$), 1.10 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found: C, 82.61; H, 7.54; N, 4.46.

B. 2-(α-*N*-Methyl-d_2-*tert*-butylaminobenzyl)-1-indenone was obtained in 80% yield as orange crystals, mp 65–67°: nmr ($CDCl_3$) δ 7.57–6.97 (m, 10 H, 9 aromatic protons + 1 vinyl proton), 5.40 (bs, 1 H, benzylic), 2.25 (m, 1 H, $-CD_2H$), 1.10 (s, 9 H, *tert*-butyl); mass spectrum 97% d_2.

C. 2-(α-*N*-Methyl-d_3-*tert*-butylaminobenzyl)-1-indenone was obtained in 50% yield as orange crystals, mp 65–67°: nmr ($CDCl_3$) δ 7.57–6.97 (m, 10 H, 9 aromatic protons + 1 vinyl proton), 5.40 (bs, 1 H, benzylic), 1.10 (s, 9 H, *tert*-butyl); mass spectrum 94.2% d_3.

The thermal decomposition and kinetic method employed were as previously described,[3,4] except the concentration of **2b** was determined spectrophotometrically at λ 321, 323, 325, and 327 nm.

Trapping Experiment. The decomposition procedure was repeated as before except that when the decomposition solution was evaporated, the distillate was condensed by means of a Dry Ice–acetone trap and then refluxed with aqueous hydrochloric acid for 2 hr. Evaporation gave a 30% yield of *tert*-butylamine hydrochloride, mp 270–285° (lit.[11] mp 270–280°).

Acknowledgment. This investigation was supported by Grant No. CA-02931 of the National Cancer Institute, United States Public Health Service.

Registry No.—**1**, 5387-50-8; **2b**, 53059-34-0; **3**, 5706-12-7; **7**, 13987-61-6; *N*-methyl-*tert*-butylamine, 14610-37-8; *N*-*tert*-butylformamide, 2425-74-3; *N*-methyl-d_2-*tert*-butylamine, 53059-35-1; *N*-methyl-*N*-nitroso-*tert*-butylamine, 2504-18-9; *N*-methyl-d_3-*N*-nitroso-*tert*-butylamine, 53059-36-2; *N*-methyl-d_3-*tert*-butylamine hydrochloride, 53059-37-3; 2-(α-*N*-methyl-d_2-*tert*-butylaminobenzyl)-1-indenone, 53059-38-4; 2-(α-*N*-methyl-d_3-*tert*-butylaminobenzyl)-1-indenone, 53059-39-5.

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Hexenopyranose Derivatives Obtained by Allylic Bromination of 6,8-Dioxabicyclo[3.2.1]oct-2-ene and 6,8-Dioxabicyclo[3.2.1]oct-3-ene and Subsequent Basic Solvolysis of the Product

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The preparation from acrolein of the two isomeric bicyclic olefins 6,8-dioxabicyclo[3.2.1]oct-3-ene (**1**, Scheme I)[3,4] and 6,8-dioxabicyclo[3.2.1]oct-2-ene (**2**)[4] has permitted the formation of the corresponding epoxides **3** and **4** from which a number of 2- and 4-monodeoxy-[3,4] and dideoxy-DL-hexopyranoses[5,6] have been prepared. Rearrangement of the epoxide **3** to the allylic alcohol **7** with *n*-butyllithium has led to the preparation of DL-glucose,[7,8] DL-allose, and DL-galactose.[9] More recently,[10] the epoxides **3** and **4** have been converted by standard procedures to the epoxides **5** and **6** respectively. Reaction of *n*-butyllithium with epoxide **4** and of lithium diethylamide with the epoxides **5** and **6** gave the allylic alcohols **9**, **8**, and **10** respectively,[10] compounds which then by well-established procedures could provide the remaining isomeric DL-aldohexoses.

The reactions employed in converting **3** to **7** and **8**, and **4** to **9** and **10**, have permitted the introduction of a functional group (OH) not only at each of the olefinic carbon atoms in **1** and **2** but also at the saturated carbon atoms C-2 and C-4 in **1** and **2**, respectively. We have now examined the allylic bromination of olefins **1** and **2** and, as well, the reaction of the resulting allyl bromide with base to determine the value of such a scheme in producing one or more of the compounds **7–10**. This paper describes the results of our findings.

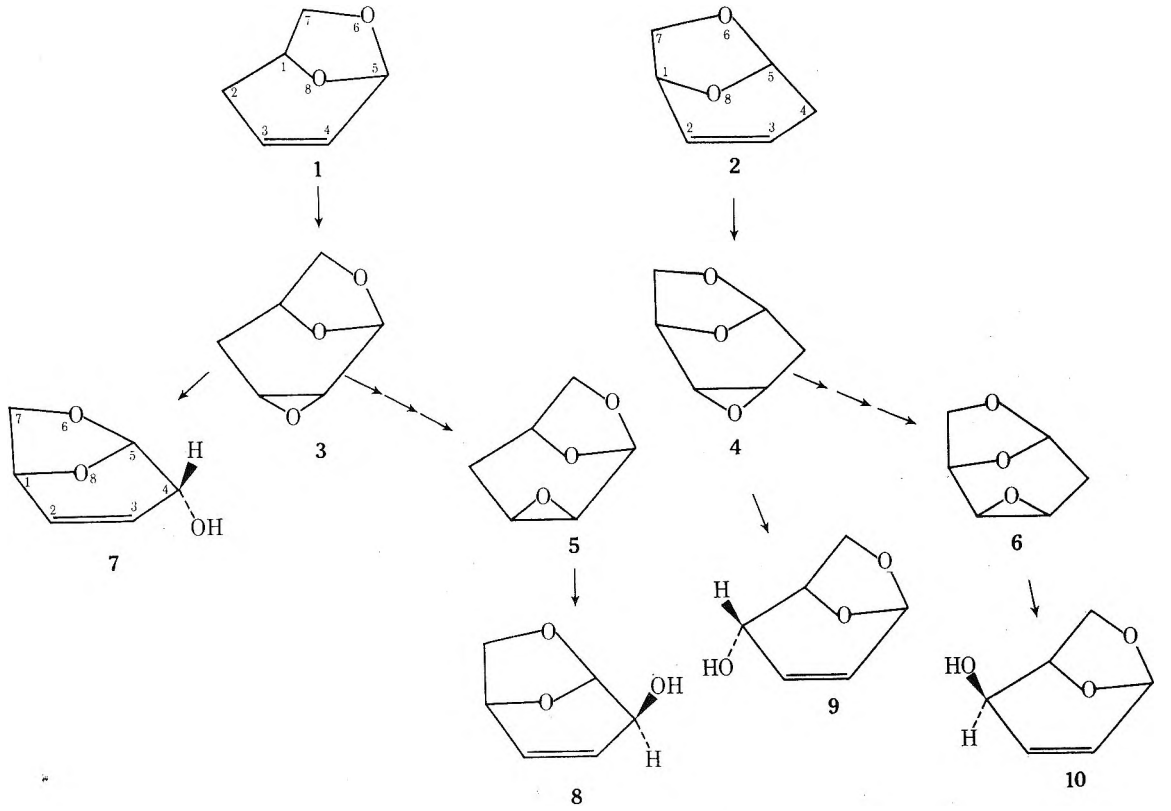
Results and Discussion

The benzoyl peroxide catalyzed reaction of *N*-bromosuccinimide (NBS) with either **1** or **2** in carbon tetrachloride gave, by final distillation, an excellent yield of 4-*exo*-bromo-6,8-dioxabicyclo[3.2.1]oct-2-ene[11] (**12**, Scheme II) of better than 98% purity according to the elemental analysis and both 100- and 220-MHz pmr spectra. Thin-layer chromatography showed only one spot. Accordingly only traces of impurity or of another isomer could be present. Analysis of the 100-MHz pmr spectrum, by double irradiation, identified the signals due to each proton and proved conclusively that the double bond was located between C-2 and C-3 of **12**. Furthermore, the narrow signal at δ 5.56 of $W/2 \approx 3.5$ Hz ($J_{5,4} \approx 0.5$ Hz, $J_{5,3} \approx 1.8$ Hz) due to the anomeric proton at C-5 provided good evidence that the proton at C-4 was endo. Thus, the Dreiding model of structure **12** showed a dihedral angle of about 85° between protons on C-4 and C-5. A small coupling is expected when the dihedral angle is in the neighborhood of 90° especially if the carbon atoms involved are also attached to highly electronegative elements. Unfortunately there was no access to the epimer of **12**, in which the proton is exo and in which the dihedral angle between the protons at C-4 and C-5 is about 35°; hence we were unable to corroborate our view concerning the exo disposition of the bromine atom at C-4, by comparison of the $J_{5,4}$ coupling in these two cases. However, we have recently prepared[10] the epimers **7** and **8** (Scheme I) by unequivocal routes. The anomeric proton of **7** at C-5 formed a dihedral angle of ~85° with the proton at C-4 and gave a narrow signal $W/2 \approx 4$ Hz ($J_{5,4} \approx 1.0$ Hz, $J_{5,3} \approx 2.0$ Hz) while the anomeric proton of **8** formed a dihedral angle of about 35° with the proton on C-4 and provided a signal which was clearly a triplet with $W/2 \approx 6.5$ Hz, $J_{5,4} \approx 3.0$ Hz, and $J_{5,3} \approx 2.0$ Hz. This comparison lends support to our view that the bromine atom in our product is exo as shown in **12**.

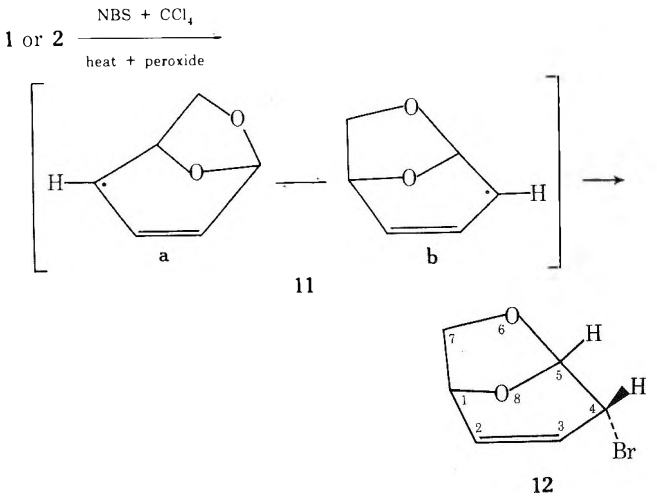
The benzoyl peroxide catalyzed bromination was clean and was completed well within 3 hr. The same product was obtained by heating the reactants in the absence of the peroxide, but these latter conditions required extensive heating for as long as 48 hr, involving a clearly apparent induction period, and resulted in concurrent polymerization and lower yields of the bromide **12**. The results obtained indicate that the reaction involves a free-radical mechanism, a view which is supported by the observation that the introduction of traces of hydroquinone markedly retards the reaction and leads to extensive decomposition during the longer heating period. The formation of apparently only one of the four possible isomers indicates a highly selective process in which **11b** (Scheme II) is the important radical species and that the endo approach of the brominating agent to C-4 is strongly inhibited by the rigidly attached 1,3-dioxolane ring.

Reaction of **12** with sodium methoxide in methanol was slow, requiring as long as 80 hr of continuous heating under reflux for completion. Shorter times gave unchanged bromide. Gas–liquid chromatography (glc) of the crude reac-

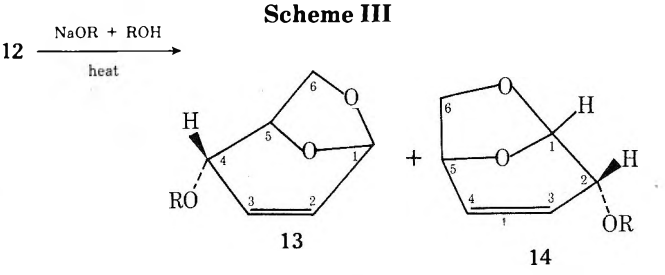
Scheme I



Scheme II



Scheme III



tion mixture showed that only two compounds **13** and **14** (R = CH_3, Scheme III) were present in the proportion 2:1, respectively. This was corroborated by the 100-MHz pmr spectrum of the crude mixture. These compounds could be separated in good yield by fractional distillation. The 100-MHz pmr spectrum of each of these two materials agreed completely with the structures shown by **13** and **14** (R = CH_3). Final confirmation that **13** (R = CH_3) was indeed 1,6-anhydro-2,3-dideoxy-4-*O*-methyl-β-DL-*erythro*-hex-2-enopyranose and **14** (R = CH_3) was 1,6-anhydro-3,4-dideoxy-2-*O*-methyl-β-DL-*erythro*-hex-3-enopyranose was obtained by comparison of their physical properties and ir and pmr spectra with those of the methyl derivatives of **13** (R = H)[10] and **14** (R = H)[7,8] each of which was obtained by unequivocal routes. No evidence could be obtained either by glc or pmr of the presence of the epimers of **13** (R = CH_3) and/or **14** (R = CH_3); hence the reaction is apparently clean and highly stereoselective.

Prolonged treatment of **12** with potassium hydroxide in water at 90° gave a 1:1 mixture of **13** and **14** (R = H) which we were unable to separate satisfactorily by either fractional distillation or column chromatography, although such separation no doubt could be achieved by tedious work. Identification of the products **13** and **14** (R = H) was made by comparison of the 100-MHz pmr spectrum of the reaction mixture with the pmr spectrum of a 1:1 mixture of authentic samples of **13** (R = H)[10] and **14** (R = H).[7,8]

Since both **13** and **14** (R = CH_3) have been found in separate experiments to be stable to the reaction conditions, their formation must occur by competitive attack by the base on **12** at C-2 and C-4. This could arise by initial slow ionization of **12** to yield an allyl carbonium ion which is then attacked by base at C-2 and C-4 from the least hindered (exo) side. The possibility exists also that some of **13** is formed by an SN2′ reaction.[12-16]

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were made by Mrs. D. Mahlow of this department. The pmr spectra (tetramethylsilane as internal standard) and decoupling experiments were made with a Varian Associates HR-100 spectrometer by Mr. G. Bigam of this department. Observed couplings are reported. The 220-MHz spectra were made by the Ontario Research Foundation, Sheridan Park, Ontario, Canada.

Glc analyses were made with a Wilkins Autoprep Model A 700, using a column ⅛ in. × 10 ft packed with a 1:1 mixture of butanediol succinate and silicone rubber SE-30 (F & M Scientific Corp.,

Avondale, Pa.), total 20%, on Carbowax 4000 (W. H. Curtin & Co., Houston, Tex.). Helium was the carrier gas at a flow rate of 60–90 cm^3/min.

The ir spectra were obtained with a Perkin-Elmer 421 grating spectrometer by Mr. R. Swindlehurst of this department.

Solvents were removed by a rotary evaporator under water pump vacuum.

Reaction of NBS with 6,8-Dioxabicyclo[3.2.1]oct-3-ene, 1, or 6,8-dioxabicyclo[3.2.1]oct-2-ene, 2. To a solution of 8.96 g (0.08 mol) of 2[4] in 400 ml of dry carbon tetrachloride was added 16.0 g (0.09 mol) of NBS along with a trace of peroxybenzoic acid catalyst. The mixture was heated under reflux for 3 hr, at which time the reaction was complete. The mixture was filtered from the supernatant succinimide and the solvent was removed from the filtrate. The residue, dissolved in 400 ml of ether, was washed thoroughly with a 10% aqueous solution of potassium carbonate and then with water. The collected water washings were extracted with ether (two 100-ml portions) and the combined ether solutions from the filtrate and extracts were dried ($MgSO_4$). Removal of the solvent and then the ether left a brown oil which was distilled in a micro fractional distillation apparatus to give 13.0 g (85%) of 4-*exo*-bromo-6,8-dioxabicyclo[3.2.1]oct-2-ene, **12**: bp 39–42° (0.05 mm), n^{25}D 1.5455.

Anal. Calcd for $C_6H_7O_2Br$: C, 37.72; H, 3.69; Br, 41.83. Found: C, 37.42; H, 3.97; Br, 42.02.

100-MHz pmr (CCl_4): δ 6.06 (d of d for H-2, $J_{1,2} \approx 4.5$ Hz, $J_{2,3} \approx 9.5$ Hz), 5.81 (d of q for H-3, $J_{3,5} \approx 1.8$ Hz, $J_{3,4} \approx 3.5$ Hz, $J_{3,2} \approx 9.5$ Hz, $J_{3,1} < 0.5$ Hz), 5.56 (narrow q for H-5, $W/2 \approx 3.5$ Hz, $J_{5,3} \approx 1.8$ Hz, $J_{5,4} \approx 0.5$ Hz), 4.68 (m for H-1, $J_{1,3} < 0.5$ Hz, $J_{1,2} \approx 4.5$ Hz), 4.63 (d of d for H-4, $J_{4,5} \approx 0.5$ Hz, $J_{4,3} \approx 3.5$ Hz, $J_{4,2} \approx 1.0$ Hz), 3.69 (two overlapping d for H-7 exo and H-7 endo, $J_{1,7\,endo} \approx 1.5$ Hz, $J_{1,7\,exo} \approx 3.0$ Hz, $J_{7\,exo,\,7\,endo} < 1.0$ Hz).

The reaction of *N,N*-dibromodimethylhydantoin with 2 gave an excellent yield of **12** as the only isolable product. Similar results were obtained by starting with compound **1**.

Reaction of 4-*exo*-Bromo-6,8-dioxabicyclo[3.2.1]oct-3-ene, 12, with Sodium Methoxide in Methanol. A solution of 5.73 g (0.03 mol) of **12** and 3.24 g (0.06 mol) of sodium methoxide in dry methanol was stirred while being heated under reflux for 80 hr. The mixture was then cooled and freed from methanol, and the residue was treated with 20 ml of water. The aqueous mixture was extracted repeatedly with ether and the combined ether extracts were dried ($MgSO_4$). Removal of the drying agent and ether gave an oily residue. Glc analysis of this crude material showed the presence of only two substances. Fractional distillation with a spinning-band column gave pure **13** (R = CH_3), bp 72–74° (2 mm), and pure **14** (R = CH_3), bp 67–69° (2 mm), in the proportion 2:1, respectively, and in a total yield of 70%. Products **13** and **14** were identical in all respects with the authentic compounds (see below).

Reaction of 4-*exo*-Bromo-6,8-dioxabicyclo[3.2.1]oct-2-ene, 12, with Aqueous Potassium Hydroxide. A mixture of the bromide **12** (7.64 g, 0.04 mol), 2.24 g (0.04 mol) of potassium hydroxide, and 100 ml of water was stirred at 90° for 48 hr and then heated under reflux for an additional 2 hr. The cooled solution was extracted continuously for 24 hr with methylene chloride. The organic layer was dried ($MgSO_4$) and then freed from solid and solvent, leaving an oily residue which distilled as a colorless oil, bp 49–53° (0.05 mm). Both glc and the pmr spectrum showed this oil to be a 1:1 mixture of only two substances. Attempts at separation by fractional distillation were unsuccessful. Glc separation resulted in decomposition of products. Only partial separation was obtained by the use of silica gel column chromatography.

The 100-MHz pmr spectrum of the mixture was identical with that of a 1:1 mixture of authentic **7**[7,8] and **9**.[10]

1,6-Anhydro-3,4-dideoxy-2-*O*-methyl-β-DL-*erythro*-hex-3-enopyranose, 14 (R = CH_3). Compound **14** (R = CH_3) was prepared by methylation of **7**[7,8] using the reported methylation procedure[17] with the following modification.

After the period of reflux, the solution was cooled and shaken with one-third of its volume of water. The aqueous layer was separated and extracted with ether (five 50-ml portions) to remove the somewhat water-soluble product. The ether extracts, combined with the organic layer from the cooled reaction mixture above, were dried ($MgSO_4$) and then freed from solid and solvent. The residue was distilled to give **14** (R = CH_3): yield 80%; bp 67–69° (2 mm); n^{25}D 1.4737.

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.43; H, 7.15.

100-MHz pmr (CCl_4): δ 6.14 (d of q for H-4, $J_{4,3} \approx 10$ Hz, $J_{4,5} \approx 4.5$ Hz, $J_{4,1} < 1.0$ Hz), 5.67 (d of q for H-3, $J_{3,4} \approx 10$ Hz, $J_{3,2} \approx 3.5$ Hz, $J_{3,5} \approx 1.8$ Hz), 5.38 (m for H-1, $W/2 \approx 4.0$ Hz, $J_{1,2} < 1.0$ Hz, $J_{1,3} \approx 2.0$ Hz), 4.56 (m for H-5, $J_{5,3} \approx 1.8$ Hz, $J_{5,4} \approx 4.5$ Hz, $J_{5,6\,endo} \approx 1.5$ Hz, $J_{5,6\,exo} \approx 2.5$ Hz), 3.52 (d for H-6 exo and H-6 endo, $J_{6\,exo,\,6\,endo} < 0.5$ Hz), 3.33 (s for CH_3), 3.21 (complex d for H-2, $J_{2,3} \approx 3.5$ Hz, $J_{1,2} < 1.0$ Hz).

1,6-Anhydro-2,3-dideoxy-4-*O*-methyl-β-DL-*erythro*-hex-2-enopyranose, 13 (R = CH_3). Compound **9**[10] was methylated by the same procedure used to prepare **14** above: yield 80%; bp 42° (0.1 mm); n^{25}D 1.4759.

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.98; H, 7.26.

100-MHz pmr (CCl_4): δ 6.04 (d of q for H-2, $J_{1,2} \approx 3.5$ Hz, $J_{2,3} \approx 10$ Hz, $J_{2,4} \approx 1.0$ Hz), 5.67 (d of q for H-3, $J_{3,2} \approx 10.0$ Hz, $J_{3,4} \approx 4.0$ Hz), at 5.34 (d for H-1, $J_{1,2} \approx 3.5$ Hz, $J_{1,3} < 0.5$ Hz), 4.58 (complex d for H-5, $J_{5,6\,exo} \approx 7.0$ Hz), 3.77 (d of d for H-6 exo, $J_{5,6\,exo} \approx 7.0$ Hz, $J_{6\,exo,\,6\,endo} \approx 8.0$ Hz), 3.35 (s for CH_3), 3.42–3.17 (complex m for H-4 and H-6 endo).

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Registry No.—1, 53152-84-4; 2, 53152-85-5; 7, 34685-53-5; 9, 52630-80-5; 12, 53111-75-4; 13 (R = Me), 53111-76-5; 14 (R = Me), 32445-57-1.

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Stereochemistry of the Reduction of α-Amino Ketones

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Received May 29, 1974

Although the stereochemistry of the reduction of α-hydroxy ketones has been extensively investigated,[2] the reduction of α-amino ketones has received very little attention. In a few instances where the reduction of α-dimethylamino ketones was reported,[3,4] only the trans amino alcohol was isolated and the stereochemistry of the reduction was not completely established. The reductions of monoalkylamino ketones with sodium borohydride have also been reported to give only trans amino alcohols except in one case involving a bicyclic ring system where a mixture of cis and trans amino alcohols was obtained.[5] The addition of Grignard reagents to acyclic amino ketones[2a,6] is known to yield products predicted by Cram's rule of "steric control

Table I
Summary of Experimental Data on the Amino Ketone Reductions

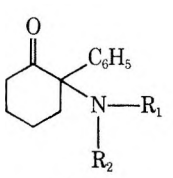
Amino ketone	Reducing agent	Solvent	Amino alcohols—Trans (%)	Amino alcohols—Cis (%)	Gc conditions[a]
1a	$NaBH_4$	EtOH	**2a** (100)	**3a** (0)	A
1b	$NaBH_4$	EtOH	**2b** (100)	**3b** (0)	A
	$Li(Me_3CO)_3AlH$	THF	**2b** (100)	**3b** (0)	A
	$LiAlH_4$	Et_2O	**2b** (100)	**3b** (0)	A
1c	$NaBH_4$	EtOH	**2c** (75)	**3c** (25)	B
	$Li(Me_3CO)_3AlH$	THF	**2c** (70)	**3c** (30)	B
	$LiAlH_4$	Et_2O	**2c** (80)	**3c** (20)	B
	B_2H_6	THF	**2c** (95)	**3c** (5)	B
1d	$NaBH_4$	EtOH	**2d** (100)	**3d** (0)	A, C
	$Li(Me_3CO)_3AlH$	THF	**2d** (100)	**3d** (0)	A, C
1e	$NaBH_4$	EtOH	**2e** (60)	**3e** (40)	B
	$Li(Me_3CO)_3AlH$	THF	**2e** (30)	**3e** (70)	B
1f	$NaBH_4$	EtOH	**2f** (100)	**3f** (0)	A
	$Li(Me_3CO)_3AlH$	THF	**2f** (100)	**3f** (0)	A
1g	$NaBH_4$	EtOH	**2g** (65)	**3g** (35)	A[b]
	$Li(Me_3CO)_3AlH$	THF	**2g** (15)	**3g** (85)	A[b]
1h	$NaBH_4$	EtOH	**2h** (100)		A[c]
1i	$NaBH_4$	EtOH	**2i** (100)		C[d]
	$Li(Me_3CO)_3AlH$	THF	**2i** (100)		C[d]

[a] The gc columns and the oven temperatures at which they were operated are the following: A, 10% phenyldiethanolamine succinate at 200°; B, 6% diglycerol at 125°; C, 15% SE 31 at 180°. [b] The structures of *trans*- and *cis*-2-(*N*-methyl-*N*-isopropyl)-2-phenylcyclohexanols are assigned tentatively on the basis of their gc retention times. [c] A small peak corresponding to *trans*-2-amino-2-phenylcyclohexanol was also obtained probably due to pyrolysis of **2h** at the injection port. [d] The reduction product was hydrogenated in the presence of 10% Pd/C and the resulting ethylamino alcohol[12] was analyzed.

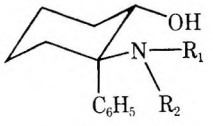
of asymmetric induction."[2a,7,8] We now report the reduction of several 2-amino-2-phenylcyclohexanones using a variety of hydride reagents. This study was undertaken to determine the stereochemistry of amino ketone reductions and to investigate the possibility of altering the stereochemical outcome by changing the substituents on the nitrogen atom or by employing different metal hydride reagents.

Results

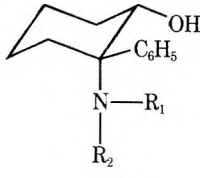
The synthesis of amino ketones **1a–f, 1h,** and **1i** has been reported previously.[4,9] 2-(*N*-Methyl-*N*-isopropyl)-2-phenylcyclohexanone (**1g**) was obtained by methylation of **1f** under Clark–Eschweiler conditions.[4] The syntheses of



1a–i



2a–i



3a–g

a, $R_1 = R_2 = H$
b, $R_1 = H$, $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$
d, $R_1 = H$, $R_2 = C_2H_5$
e, $R_1 = CH_3$, $R_2 = C_2H_5$
f, $R_1 = H$, $R_2 = i\text{-}C_3H_7$
g, $R_1 = CH_3$, $R_2 = i\text{-}C_3H_7$
h, $R_1 = H$, $R_2 = tert\text{-}C_4H_9$
i, $R_1, R_2 = -CH_2CH_2-$

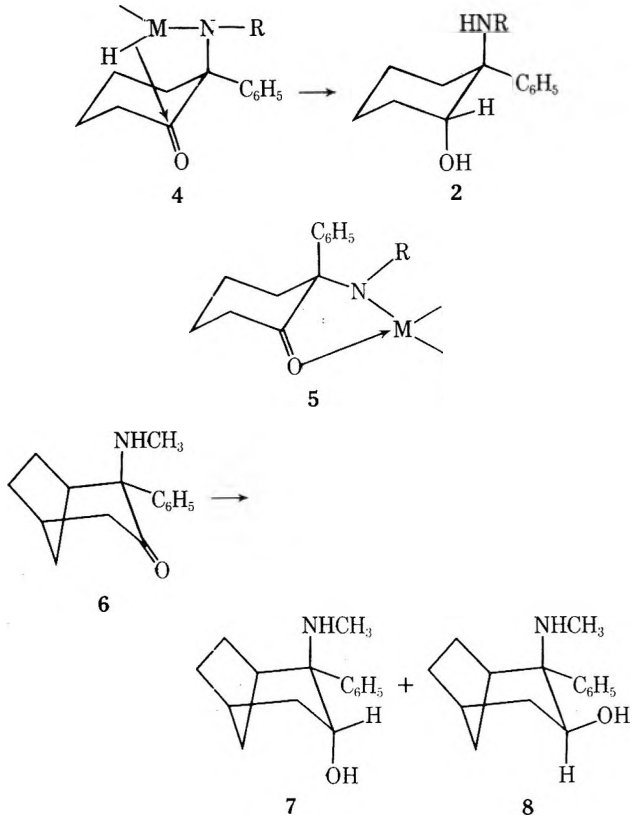
trans amino alcohols **2a–c, i** and the cis amino alcohols **3a, b** have also been recorded and their structures established.[4,9] The cis dimethylamino alcohol, **3c**, was prepared by the treatment of **3b** with ethyl chloroformate followed by reduction of the intermediate carbamate with diborane. Treatment of **2a** with acetic anhydride in pyridine and reduction of the resulting diacetate with diborane in tetrahydrofuran provided **2d** which was identical with a sample prepared by the reduction of **1d** with sodium borohydride.[4] Similarly, the cis ethylamino alcohol **3d** was obtained by acetylation of **3a** followed by reduction with diborane. The tertiary amino alcohols **2e** and **3e** were prepared by treatment of the corresponding ethylamino alcohols **2d** and **3d** with ethyl chloroformate and subsequent reduction of the carbamates with lithium aluminum hydride. Condensation of **2a** with acetone in the presence of *p*-toluenesulfonic acid and reduction of the imine gave the trans isopropylamino alcohol **2f** with the same characteristics as reported earlier.[4] The cis isomer **3f** was synthesized from **3a** by first treating it with 2,2-diethoxypropane in the presence of a small amount of *p*-toluenesulfonic acid followed by reduction of the intermediate oxazolidine with diborane. The *tert*-butylamino alcohol **2h** which was obtained by the reduction of amino ketone **1h** with sodium borohydride in ethanol[4] was shown to have trans configuration by its treatment with constant-boiling hydrobromic acid when the only basic material formed was *trans*-2-amino-2-phenylcyclohexanol (**2a**). Reduction of aziridino ketone **1i** with sodium borohydride provided *trans*-2(1-aziridinyl)-2-phenylcyclohexanol (**2i**) the stereochemistry of which was established by its hydrogenation in the presence of 10% palladium on carbon to give the trans ethylamino alcohol **2d**.[9]

The amino ketones were reduced with various reagents as listed in Table I. The crude reduction products were analyzed by gas chromatography and the components were identified and their ratios determined by comparison with standard mixtures of trans and cis amino alcohols previously synthesized. The results are summarized in Table I.

Discussion

It is clear from Table I that the primary and secondary amino ketones are reduced exclusively to the trans amino alcohols irrespective of the reducing agents used. This indicates that a stable complex (**4**) between the amine and the reducing agent is formed[10] and the reduction of the carbonyl group takes place by an internal hydride transfer.[11] It appears that the cyclic intermediate (**5**) as suggested in the reductions of α-hydroxy ketones by Cram and coworkers[2,7,8] is not a significant factor in these reductions. In the case of the bicyclic amino ketone **6**, the internal hydride transfer is hindered by the two-carbon bridgehead resulting in the reduction of the carbonyl group from both sides

giving a mixture of trans and cis amino alcohols, 7 and 8, respectively.



The nonstereoselectivity in the reduction of tertiary amino ketones may be explained as follows. The complex formed between the tertiary amine and the reducing agent is not as stable as that between a secondary amine and the reducing agent because a covalent bond is not possible in the former case. Consequently, the reduction of the keto group takes place both by hydride transfer and from hydride ions in solution. As the size of the substituents on the N atom and/or the reducing agent is increased, the stability of the amine-reducing agent complex is further weakened. In addition, a bulky amino group or a large reducing agent will hinder the approach of the hydride from the direction of the amine function, thus producing more of the cis amino alcohol.[12] This view is supported by the results of the reduction of amino ketones **1c**, **1e**, and **1g** with sodium borohydride and lithium tri-*tert*-butoxyaluminum hydride. The difference of the trans:cis ratio in the reduction of **1c** with sodium borohydride in methanol and diborane in tetrahydrofuran is due to the greater stability of the amine–borate complex in a nonhydroxylic solvent. The absence of the formation of a cis amino alcohol in the reduction of the aziridinyl ketone **1i** indicates that the complex between the aziridinyl group and the reducing agent is strong enough to effect the reduction almost exclusively by internal hydride transfer. The small, compact size of the aziridinyl group is probably responsible for the increased stability of this amine-reducing agent complex.[13]

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Thin-layer chromatography was performed using silica gel H from Brinkman Instruments coated on 5 × 15 cm glass plates. The developing solvent was $CHCl_3$–MeOH (9:1) unless otherwise mentioned. Compounds were detected by development with iodine vapor. Gas chromatographic analyses were performed on a F&M model 810 instrument fitted with a thermal conductivity detector. The columns used are given in Table I. The solid support was non-acid-washed chromosorb W. The nmr spectra were obtained using a Varian A-60 spectrometer with TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 237B grating spectrophotometer. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

2-(*N*-Methyl-*N*-isopropylamino)-2-phenyleyclohexanone (1g). A mixture of 86 mg (0.38 mmol) of amino ketone **1f**, 0.5 ml of 37% aqueous formaldehyde, and 4 ml of formic acid was heated on a steam bath for 24 hr. A tlc analysis indicated that the reaction was complete. The cooled mixture was diluted with 20 ml of H_2O, 0.5 ml of 6 *N* HCl was added, and then the mixture was extracted with ether to remove any neutral materials. The aqueous solution was made basic with NaOH, extracted with ether, dried (K_2CO_3), and evaporated to dryness to give **1g** as an oil. It was treated with picric acid in ether and the picrate salt was recrystallized from ethanol–ether to give 107 mg (64%), mp 190–192°.

Anal. Calcd for $C_{22}H_{26}N_4O_8$: C, 55.69; H, 5.52; N, 11.80. Found: C, 55.40; H, 5.66; N, 11.68.

***trans*-2-(*N,N*-Dimethylamino)-2-phenylcyclohexanol (2c) Hydrochloride.** Amino alcohol **2c** was prepared from *trans*-2-(*N*-methylamino)-2-phenylcyclohexanol (**2b**) by Clark–Eschweiler methylation as described previously.[4] It was converted to its hydrochloride and recrystallized from ethanol–ether; mp 220–221°.

Anal. Calcd for : C, 65.73; H, 8.67; Cl, 13.86; N, 5.47. Found: C, 65.98; H, 8.97; Cl, 13.86; N, 5.45.

***trans*-2-(*N*-Ethylamino)-2-phenylcyclohexanol (2d).** A solution of 100 mg (0.53 mmol) of **2a** in 5 ml of pyridine was acetylated with 0.5 ml of acetic anhydride overnight. The volatile materials were removed under reduced pressure; the residue was dissolved in ether; the ether solution was washed with water, dried (Na_2SO_4), and evaporated to dryness. The crude *O,N*-diacetate was dissolved in 10 ml of anhydrous THF, the solution was cooled to 0°, 8 ml of a 1 *M* solution of B_2H_6 in THF was added, and the mixture was heated under reflux for 2 hr under a nitrogen atmosphere. A cold, saturated solution of NH_4Cl was carefully added to the cooled solution followed by 6*N* HCl to break up any borate complex. The solvents were removed *in vacuo;* the residue was dissolved in 15 ml of water and extracted with $CHCl_3$ to remove neutral materials. The aqueous solution was made basic with NaOH, extracted with $CHCl_3$, dried (K_2CO_3), and evaporated to dryness. The residue was dissolved in ether and converted to the hydrochloride salt to give 75 mg (55% for two steps) of **2d** as its hydrochloride, mp 205–207°, after recrystallization from ethanol–ether. A mixture melting point with the $NaBH_4$ reduction product[4] of **1d** was undepressed.

***trans*-2-(*N*-Ethyl-*N*-methyl)-2-phenylcyclohexanol (2e).** A mixture of 130 mg (0.6 mmol) of amino alcohol **2d** in 10 ml of $CHCl_3$, 1.0 ml of ethyl chloroformate, and 150 mg of $NaHCO_3$ was stirred at room temperature for 3 hr. A tlc analysis showed that the reaction was complete. The inorganic materials were removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in 15 ml of dry THF, 150 mg of $LiAlH_4$ was added, and the mixture was heated under reflux for 3 hr. The product after the usual work-up was characterized as the hydrochloride salt (105 mg, 65%), mp 219–220° dec.

Anal. Calcd for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.86; Cl, 13.14; N, 5.19. Found: C, 66.16; H, 9.09; Cl, 13.53; N, 5.19.

***trans*-2-(*N*-*tert*-Butylamino)-2-phenylcyclohexanol (2h).** A mixture of 140 mg (0.5 mmol) of 2-(*N*-*tert*-butylamino)-2-phenylcyclohexanone (**1h**) hydrochloride[4] in 10 ml of ethanol and 100 mg of $NaBH_4$ was stirred at room temperature for 3 days. The product was isolated by the usual work-up and converted to the HCl salt to give 96 mg (69%) of **2h** as its hydrochloride salt, mp 202–203° dec. A mixture melting point with a sample prepared previously[4] was undepressed.

Anal. Calcd for $C_{16}H_{25}ClNO$: C, 67.90; H, 9.25; Cl, 12.49; N, 4.93. Found: C, 67.10; H, 9.15; Cl, 12.76; N, 4.93.

A solution of 96 mg (0.34 mmol) of **2h** (HCl) in 10 ml of constant-boiling hydrobromic acid was heated at 110° for 10 hr. The cooled mixture was diluted with water and extracted with ether to remove neutral by-products, mostly 2-phenylcyclohexanone.[14] The aqueous solution was made basic with NaOH, extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue on analysis by gc showed only one component corresponding to *trans*-2-amino-2-phenylcyclohexanol (**2a**). It was converted to the HCl salt to give 24 mg (32%) of **2a** (HCl), mp 199–200°. A mixture melting point with an authentic sample[4] was not depressed.

***cis*-2-(*N,N*-Dimethylamino)-2-phenylcyclohexanol (3c).** A mixture of 205 mg (1 mmol) of **3b** as the free base in 20 ml of $CHCl_3$, 2.5 ml of ethyl chloroformate, and 300 mg of $NaHCO_3$ was stirred at room temperature for 3 hr. The inorganic materials were

filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 25 ml of THF, 7 ml of a 1 *M* solution of B_2H_6 in THF was added, and the mixture was heated under reflux for 2 hr under a nitrogen atmosphere. Isolation of the product as described for the preparation of **2d** and conversion to the HCl salt gave 230 mg (90%) of **3c** (HCl), mp 204–206° dec.

Anal. Calcd for $C_{14}H_{22}ClNO$: C, 65.73; H, 8.67; Cl, 13.86; N, 5.47. Found: C, 65.96; H, 8.98; Cl, 13.57; N, 5.51.

***cis*-2-(*N*-Ethylamino)-2-phenylcyclohexanol (3d).** Acetylation of 193 mg (1 mmol) of **3a** with acetic anhydride in pyridine followed by reduction of the resulting *O,N*-diacetate with B_2H_6 in THF as described for the synthesis of **2d** gave 130 mg (59%) of **3d** as the free base, mp 99–100°, after recrystallization from hexane.

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.37. Found: C, 76.90; H, 9.74; H, 6.53.

***cis*-2-(*N*-Ethyl-*N*-methylamino)-2-phenylcyclohexanol (3e).** This compound was prepared from 60 mg (0.27 mmol) of **3d** using the same procedure for the conversion of **2d** to **2e**. The product was converted to the HCl salt (44 mg, 60%), mp 205–206°.

Anal. Calcd for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.86; Cl, 13.14; N, 5.19. Found: C, 66.67; H, 8.75; Cl, 13.13; N, 5.10.

Amino Ketone Reductions. In reductions with sodium borohydride, the free base was dissolved in ethanol, the solution was cooled to 0°, $NaBH_4$ was added in small portions, and the mixture was stirred overnight. After establishing the completion of the reaction by tlc, the mixture was diluted with water and acidified with 6 *N* HCl. The solvents were removed *in vacuo;* the residue was redissolved in water and extracted with ether. The aqueous layer was made basic with NaOH, extracted with ether, dried (K_2CO_3), and evaporated to dryness. When lithium tri-*tert*-butoxyaluminum hydride[15] was used as the reducing agent, the reductions were carried out in dry THF and the reagent was added in one lot. Otherwise the conditions were the same as for $NaBH_4$ reductions. In the case of $LiAlH_4$ reductions, ether was used as the solvent and the excess hydride was decomposed with wet ether. Amino ketone **1c** was also reduced with diborane. The procedure used is described under the synthesis of *trans*-2-(*N*-ethylamino)-2-phenylcyclohexanol (**2d**).

The reduction products without any further purification were analyzed by gc. The ratio of trans and cis amino alcohols was estimated from integration of the peaks corresponding to each component. Analysis of standard mixtures showed that this type of estimation was accurate within ±5%.

Registry No.—**1a,** 7015-50-1; **1b,** 7063-30-1; **1c,** 7015-60-3; **1d,** 6740-82-5; **1e,** 7062-18-2; **1f,** 7015-55-6; **1g,** 52906-46-4; **1g** picrate, 52906-47-5; **1h,** 52906-48-6; **1h** HCl, 7015-19-2; **1i,** 35099-65-1; **2a,** 52906-49-7; **2a** HCl, 7015-63-6; **2b,** 10275-95-3; **2c** HCl, 52906-50-0; **2d,** 52906-51-1; **2d** HCl, 7141-86-8; **2e** HCl, 52951-31-2; **2f,** 7015-72-7; **2g,** 52906-52-2; **2h** HCl, 7015-67-0; **2i,** 35099-66-2; **3a,** 52906-53-3; **3b,** 7015-29-4; **3c** HCl, 52949-44-7; **3d,** 52906-54-4; **3e** HCl, 52906-55-5; **3g,** 52906-56-6.

References and Notes

(1) Taken in part from the Ph.D. dissertation of K. J. TerBeek, Wayne State University, 1974.
(2) See for example: (a) D. J. Cram and F. A. A. Elhafez, *J. Amer. Chem. Soc.*, **74,** 5828 (1952); (b) J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *ibid.*, **82,** 3913 (1960).
(3) M. Mousseron and M. Canet, *Bull. Soc. Chim. Fr.*, **18,** 792 (1951).
(4) C. L. Stevens, A. B. Ash, A. Thuillier, J. H. Amin, A. Balys, W. E. Dennis, J. P. Dickerson, R. P. Glinski, H. T. Hanson, M. D. Pillai, and J. W. Stoddard, *J. Org. Chem.*, **31,** 2593 (1966).
(5) C. L. Stevens, T. A. Treat, P. M. Pillai, W. Schmonsees, and M. D. Glick, *J. Amer. Chem. Soc.*, **95,** 1978 (1973).
(6) B. M. Benjamin, H. J. Schaffer, and C. J. Collins, *J. Amer. Chem. Soc.*, **79,** 6160 (1957).
(7) D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81,** 2748 (1959).
(8) D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.*, **85,** 1243 (1963).
(9) C. L. Stevens, J. M. Cahoon, T. R. Potts, and P. M. Pillai, *J. Org. Chem.*, **37,** 3130 (1972).
(10) Stable borane–amine complexes have been isolated and used in the reduction of ketones in protic solvents. See, for example, (a) H. C. Kelly, M. G. Guisto, and F. R. Marchelli, *J. Amer. Chem. Soc.*, **86,** 3882 (1964); (b) S. S. White, Jr., and H. C. Kelly, *ibid.*, **90,** 2009 (1968); **92,** 4303 (1970).
(11) A similar mechanism has been proposed for the reduction of some steroidal ketones: (a) E. C. Presterfield and D. M. S. Wheeler, *J. Org. Chem.*, **30,** 1513 (1965); (b) P. T. Lansbury, J. F. Bieron, and M. Klein, *J. Amer. Chem. Soc.*, **88,** 1477 (1966).
(12) M. Akhtar and S. Marsh [*J. Chem. Soc. C,* 937 (1966)] have argued similarly to explain their results in the reduction of cholestan-5-α-ol-3-one.
(13) D. E. McLaughlin, M. Tamres, S. Searles, Jr., and F. Block [*J. Inorg. Nucl. Chem.*, **18,** 118 (1961)] isolated an *N*-methylaziridinetrimethylboron complex and showed that it was more stable than the complexes of trimethylboron with other cyclic tertiary amines.
(14) J. W. Stoddard, M. S. Thesis, Wayne State University, 1967.
(15) Purchased from Alfa Inorganics, Beverly, Mass.

The π-Electron Steric Effect

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The study of substituent proximity effects and their influence on molecular properties have provided considerable information concerning the various contributory factors of these substituents and many of these studies have produced quantitative relationships which account for the influence of these factors.[1,2] On the other hand, Byron and his coworkers have reported[3] a nonquantitative, acid-weakening proximity effect of 2′-substituents in 2′-substituted biphenyl-4-carboxylic acids relative to a "normal" effect of 3′ and 4′ substituents in the corresponding 3′- and 4′-substituted biphenyl-4-carboxylic acids[4] and Dell'Erba and his coworkers have reported[5] similar observations for the rates of the piperidine-induced debromination of 2′-substituted 3-nitro-4-bromobiphenyls relative to the rates of debromination for the 3′- and 4′-substituted derivatives.[6] However, both groups of workers conclude that similar effects are not general for the 2′-substituted biphenyl system but rather depend upon the nature of the reaction center at the 4 position. This conclusion seems unlikely since the electron density about any reaction center at the 4 position should be altered by 2′ substituents if significant interactions, possibly of a π-electron steric origin, occur between the 2′ substituent and the π electrons of the ring carrying the reaction center. As an amino group would less readily accept an increase in electron density compared to the carboxylic acid, bromo, or other electronegative center, a study utilizing the amino group as the reaction center would be particularly suitable for investigating the π-electron steric effect of 2′ substituents in the biphenyl system. This paper reports such a study based on comparative pK_a values for a series of 2′- and 4′-substituted 4-aminobiphenyls and 4′-substituted 3-aminobiphenyls. In these series, "normal" alterations in pK_a should be produced by the 4′ substituents and also by the 2′ substituents if indeed a π-electron steric effect is insignificant.

The pK_a data for the three series of substituted aminobiphenyls are reported in Tables I and II. Inspection of these data indicates that the order and magnitude of the pK_a's for the two 4′-substituted series are identical within experimental error and can be rationalized in terms of expected, typical substituent effects. Correlation analyses[7,8] of the pK_a's *via* the Hammett equation gives $\rho = -0.67$, correlation coefficient $r = 0.930$, and standard deviation $s = 0.12$ for the 4′-substituted 4-aminobiphenyls and $\rho = -0.69$, $r = 0.939$, $s = 0.12$ for the 4′-substituted 3-aminobiphenyls. However, the pK_a data for the 2′-substituted 4-aminobiphenyls do not give a quantitative fit to the Hammett equation nor are the order and magnitude of these pK_a's "normal." That is, the 2′-acetamido group is base weakening relative to base strengthening by the 4′-acetamido groups, the 2′-hydroxy group is more strongly base strengthening than a 4′-hydroxy or methoxy group, and the 2′-nitro group is considerably less base weakening than in the 4′ position. These differences are attributed to a π-electron steric alteration in the "normal" effect of a substituent when the substituent is in the 2′ position.

Table I
pK_a's for 2'- and 4'-Substituted 4-Aminobiphenyls in 10% Ethanol–Water at 20°

Substituent[f]	pK_a	Substituent[g]	pK_a
H	4.27[a]	2'-NO_2	4.00[c]
2'-$NHCOCH_3$	4.19	4'-NO_2	3.59[d]
4'-$NHCOCH_3$	4.30	4'-F	4.27
2'-OH	4.39	4'-$COCH_3$	3.89[e]
4'-OH	4.29[b]		

[a] 4.27 in water: H. C. Brown, D. H. McDaniel, and O. Hafliger, "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N.Y., 1955, pp 567–662. 4.05 in 50% ethanol, ref 4. 3.94 in 70% ethanol, ref 26. [b] 4.44 in 50% ethanol: E. Czerwinska-Fejgin and W. Polaczkowa, *Rocz. Chem.*, **41**, 1759 (1957). [c] 3.63 in 50% ethanol, ref 3. [d] 3.48 in 50% ethanol, ref4. [e]3.97 in 50% ethanol, reference in footnote *b*. [f] Registry numbers are, respectively, 53059-26-0; 3366-61-8; 21849-92-3; 1204-79-1; 1140-28-9. [g] Registry numbers are, respectively, 1211-40-1; 324-93-6; 1141-39-5.

Table II
pK_a's for 4'-Substituted 3-Aminobiphenyls in 10% Ethanol–Water at 20°

Substituent[c]	pK_a	Substituent[d]	pK_a
H	4.22[a]	OCH_3	4.31[b]
$NHCOCH_3$	4.37	NO_2	3.64[b]
Br	4.17		

[a] 4.18 in water: H. C. Brown, D. H. McDaniel, and O. Hafliger, "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N.Y., 1955, pp 567–662. 3.82 in 50% ethanol; J. J. Elliott and S. F. Mason, *J. Chem. Soc.*, 2352 (1959). 3.89 in 70% ethanol, ref 26. [b] Determined in 12.5% ethanol–water. [c] Registry numbers are, respectively, 2243-47-2; 53059-27-1; 40641-71-2. [d] Registry numbers, are, respectively, 53059-28-2; 53059-29-3.

The "normal" effect of an acetamido group is resonance electron donating and inductive (and/or field) electron withdrawing with the resonance effect usually being predominant. However, the 2'-acetamido 4-aminobiphenyl derivative is a weaker base than the parent compound unlike the 4'-acetamido derivative which is a slightly stronger base. In the 2' position the acetamido group is sterically prohibited from exerting its resonance effect but is able to assume a minimal-repulsive, nonresonance conformation with respect to the π electrons of the adjacent ring. As a consequence, the predominant effect of the 2'-acetamido group on the adjacent ring is one of base weakening electron withdrawal. In the case of the hydroxy derivatives, a 4'-hydroxy group has little effect on the base strength of the parent compound while the 2'-hydroxy group increases the base strength by some 0.10–0.12 pK units. The "normal" effect of the hydroxy group is the same as that of the acetamido. The greater base strength of the 2'-hydroxy derivative is apparently due to the interaction of the unshared electron pairs on the oxygen of the 2'-hydroxy group with the π electrons of the ring carrying the amino group. This interaction causes a displacement of the π electrons toward the amino group and has the effect of increasing the electron density about the amino group and thus its basicity in the 2'-hydroxy derivative relative to the 4' derivative. The basicities of the nitro derivatives, as expected, are all less than that of the parent compounds. The effect of a 4'-nitro group is "normal," *i.e.*, it is able to exert both its base-weakening resonance and inductive/field electron-withdrawing effects. However, the 2'-nitro group is sterically prohibited from exerting its resonance electron-withdrawing effect and it would be expected, as was observed, that the 2'-nitro derivative should be more basic than a 4'-nitro derivative. However, the difference in pK_a between the 2'- and 4'-nitro derivatives (0.36–0.41 pK units) is considerably greater than expected when one considers the rather small transmission coefficient of 0.23–0.24 for the 1,1' bond in 4'-substituted 3- and 4-aminobiphenyls. That is, polar substituent effects are transmitted only *ca.* 23–24% as effectively from the 4' position of biphenyl to the amino group *via* the 1,1' bond as they are from the 3 or 4 position to the amino group in substituted anilines.[10] The unexpected magnitude of this difference in pK_a's for the nitro derivatives arises because the 2'-nitro group cannot assume a repulsion-free, nonresonance conformation with respect to the π electrons on the adjacent ring. As a result, the 2'-nitro group's electron-withdrawing inductive/field effect is offset by a displacement of the π electrons of this ring toward the amino group. This π-electron steric interaction has the effect of decreasing the 2'-nitro group's base-weakening ability and increasing the difference in base strength between the 2'-nitro and 4'-nitro derivatives. A similar effect is apparently responsible for the facile polarographic reduction of the 2'-nitro group relative to a 4' nitro in a series of 4-substituted 2'- and 4'-nitrobiphenyls.[12]

The results of this study support the existence of a π-electron steric effect and suggest that such an effect is probably general for appropriately substituted 2'-biphenyl and related systems.

Experimental Section

The 2'- and 4'-substituted 4-aminobiphenyls and two of the 4'-substituted 3-aminobiphenyls were prepared as previously reported in the literature and were recrystallized several times from appropriate solvents to a constant melting point in agreement with the values reported previously.[13] The remaining 4'-substituted 3-aminobiphenyls were prepared as described below.

4'-Nitro-3-aminobiphenyl. 3-Aminobiphenyl (2 g, 0.0118 mol) (obtained from reduction of 3-nitrobiphenyl[14,15]) was dissolved with stirring in 30 ml of concentrated H_2SO_4 while the temperature was maintained below 30°. The solution was cooled to −5° and 1.2 g (0.0119 mol) of KNO_3 was added in increments to the stirred solution so that the temperature did not rise above 0°. After addition of the KNO_3, the reaction mixture was stirred for 2 hr while maintaining the temperature below 0° and was then poured onto 400 g of ice. When the ice had melted, the solution was filtered and the collected solid was recrystallized twice from ethanol to give 1.64 g (65%) of 4'-nitro-3-aminobiphenyl (orange needles) with mp 135–136° (lit.[16] mp 137°).

4'-Acetamido-3-aminobiphenyl. 3-Nitrobiphenyl (obtained from the coupling of the diazonium acetate of *m*-nitroaniline and benzene[14]) was subjected to Friedel-Crafts acetylation[17] to obtain 4'-acetyl-3-nitrobiphenyl.[18] This material was converted to the oxime[17,19] and subjected to a PCl_5-induced Beckmann rearrangement[17] to give 4'-amino-3-nitrobiphenyl[20] which was then acetylated with a glacial acetic acid–acetic anhydride mixture to give 4'-acetamido-3-nitrobiphenyl.[21] The acetamido compound (2 g, 0.008 mol) was dissolved in 100 ml of 95% ethanol and placed on a Parr hydrogenator for 12 hr at 60 psi H_2 in the presence of a catalytic amount of PtO_2. Normal work-up followed by several recrystallizations from ethanol–water yielded 0.33 g (19%) of 4'-acetamido-3-aminobiphenyl with mp 135–136°. *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.10; H, 6.05; N, 12.25.

4'-Methoxy-3-aminobiphenyl. 4'-hydroxy-3-nitrobiphenyl (yellow crystals, mp 224–226°; *Anal.* Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 67.04; H, 3.98; N, 6.49) was prepared from 4'-amino-3-nitrobiphenyl by a procedure reported previously by Bell and Kenyon[22] for the 4,4' derivative and 4'-methoxy-3-nitrobiphenyl (yellow needles, mp 174–175°; *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68,04; H, 4.84; N, 6.01) was prepared from the 4'-hydroxy compound by a procedure reported previously by Copp and Walls.[23] The 4'-methoxy-3-nitrobiphenyl compound (0.32 g, 0.0014 mol) was dissolved in 100 ml of hot 95% ethanol and placed on a Parr hydrogenator for 48 hr at 60 psi H_2 in the presence of a catalytic amount of PtO_2. The solution was then filtered and the alcohol was evaporated under vacuum. The oily residue was dissolved in 6 *N* HCl and the solution was stirred 1 hr at room temperature and then was reduced to −5°.

NH_4OH (6 *N*) was added at this temperature and the resulting yellow solid was collected. This material turns brown on standing in air or in solution. If placed in a desiccator under vacuum, the original yellow solid slowly turns brown over a period of several days. The yellow material, after 1 day in the desiccator, melted sharply at 75°. An analysis of this compound, assumed to be the 4′-methoxy-3-aminobiphenyl, could not be obtained. However, the uv–visible, nmr, and pK_a were consistent with those of the other 4′-substituted 3-aminobiphenyls.

Measurement of pK_a's. The pK_a's of the substituted 4-aminobiphenyls and those of three of the substituted 3-aminobiphenyls were determined spectrophotometrically[24] using a Beckman DK-2 recording spectrophotometer. Stock solutions (3×10^{-3} *M*) of these compounds (except 3-aminobiphenyl which was 1×10^{-3} *M*) were prepared by dissolving a weighed sample of each amine in 50 ml of absolute ethanol and diluting to 100 ml with deionized water. Spectra solutions (6×10^{-4} *M*; 3.5×10^{-4} for 3-aminobiphenyl) were then prepared by diluting one part of the stock solution with four parts of deionized water, buffer solution, or concentrated hydrochloric acid to form the basic, intermediate, and acid solutions, respectively. In all cases, the alcohol content of the spectra solutions was 10%.

The pK_a's were calculated from eq 1[24] where A_B represents the absorbance of the basic solution, A_A is the absorbance of the concentrated HCl solution, and A is the absorbance of an intermediate buffered acidic solution. The buffered solutions were prepared

$$pK_a = pH - \log\frac{A - A_A}{A_B - A} \quad (1)$$

using Clark and Lubs hydrochloric acid buffers[25] and their pH's were measured on a Leeds and Northup research pH meter. The medium shift was minimal in all cases and the absorbance of all solutions was measured at the wavelength at which A_B was measured.

The pK_a's of the 4′-methoxy- and 4′-nitro-3-aminobiphenyls, due to solubility (nitro compound) or experimental difficulties (methoxy compound), were determined potentiometrically by measuring the pH of a solution containing exactly equivalent amounts of the amine and its salt.[26] Amine (40–50 mg) was weighed accurately into a weighing boat and then transferred to a 100-ml beaker with 10 ml of absolute ethanol. Water (70 ml) was added and the solution was stirred to ensure complete solubility of the amine. The calculated amount of 0.0977 *N* HCl needed to half-neutralize the amine present was added to the solution with a micropipet and the pH of the resulting solution was then read.

The pK_a's reported in Tables I and II are the average obtained from at least four determinations (except the 4′-methoxy- and 4′-nitro-3-aminobiphenyls which represent the average of two determinations). The maximum deviation from the mean of replicate pK_a values did not exceed 1.4% except in the case of 4′-fluoro-4-aminobiphenyl (3.3%).

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Registry No.—3-Nitrobiphenyl, 2113-58-8; 4′-hydroxy-3-nitrobiphenyl, 53059-30-6; 4′-methoxy-3-nitrobiphenyl, 53059-31-7.

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Electrophilic Substitution on Metallocenes. Reactivity of the Ferrocene System in Protodeboronation and Protodesilylation

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The determination of the electrophilic reactivity of ferrocene relative to benzene has been carried out only in a few instances, such as mercuration and H–D exchange.[1,2] A major difficulty is the tendency of ferrocene to oxidation, which may interfere with the rate measurements even in those reactions where the electrophile is not a direct oxidizing agent. Thus, previous rate measurements concerning the protodesilylation reaction[3] seemed to be misled by oxidation (*vide infra*). We now wish to report rate data for the protodeboronation of ferrocenylboric acid (compound I) and the protodesilylation of trimethylsilylferrocene (compound II) as obtained under conditions whereby the incursion of side reactions could be neglected. Such data yield two independent assessments of the very high electrophilic reactivity of the ferrocene system relative to benzene.

Product analysis showed that ferrocenylboric acid was cleaved quantitatively in 5 min by 10% sulfuric acid in a 1:2 v/v water–ethanol mixture at 50°. Accordingly, on quenching with a saturated Na_2CO_3 aqueous solution, ferrocene was isolated by standard methods in 96% yield.

The reaction rate was determined under N_2 atmosphere at several acid concentrations by measuring the absorbance *decrease* in the electronic spectrum accompanying the replacement of the boric functional group by hydrogen at 440 nm. Oxidation, which eventually set in, was accompanied by an absorbance *increase*. Infinity time determinations were obtained by Mangelsdorf's method.[4] The reaction followed strictly first-order kinetics and the results were duplicated with a satisfactory degree of reproducibility under all tested conditions.

Trimethylsilylferrocene behaved similarly both from the point of view of reactivity in acidic mixed aqueous solvents and from the spectral features. These observations were clearly at variance with those reported by Marr and Webster,[3] who presumably followed the *slower*, subsequent oxidation reaction (absorbance increase) and did not correlate their product analysis (4-hr run under reflux) with the actual rate process. In fact, we found that trimethylsilylferrocene underwent complete electrophilic replacement by pro-

Table I
Dependence of First-Order Rate Constants for the Reaction of Ferrocenylboric Acid and Trimethylsilylferrocene on Acid Concentration

Protodeboronation[a]		Protodesilylation[b]	
% H_2SO_4	$10^4 \times k$, sec^{-1}	HCl, M	$10^3 \times k$, sec^{-1}
10	6.56	0.050	2.99
15	13.6	0.080	3.93
16	24.7	0.120	6.12
18	42.9	0.157	7.81
20	60.8	0.253	12.6
21	145	0.405	24.7
25	955	0.600	30.8

[a] λ 440 nm; t = 44.7°; 1:2 v/v H_2O–EtOH. [b] λ 328 nm; t = 55.2°; 1:4 v/v H_2O–CH_3OH.

Experimental Section

Trimethylsilylferrocene and ferrocenylboric acid were prepared by the methods reported in the literature.[12,13] Their structure and purity were checked by elemental analysis and electronic, infrared, and nmr spectra.

The product analysis for the protodesilylation reaction was performed as follows. Trimethylsilylferrocene (0.5 g, 2 mmol) was dissolved in 150 ml of a 1 M HCl solution in 1:4 v/v water–methanol mixture and warmed at 50° for 4 min. Then the solution was poured in a cold, Na_2CO_3-saturated aqueous solution, which was repeatedly extracted with petroleum ether. The ether layer was concentrated by evaporation and chromatographed on alumina with petroleum ether as eluent. Ferrocene was obtained in 96% yield and identified by elemental analysis, melting point (173–174°, lit.[14] 174°), and nmr spectrum.

As to the protodeboronation reaction, ferrocenylboric acid (0.24 g, 1.05 mmol) was made to react in 500 ml of 10% sulfuric acid solution in 1:2 v/v water–ethanol at 50°. The reaction time was 5 min, and ferrocene was isolated in 96% yield.

The rate measurements were made by recording the absorbance decrease of the reacting solutions at λ 328 and 440 nm for the protodesilylation and protodeboronation reactions, respectively. A Beckman Model DB-GT self-recording spectrophotometer was used with a tenfold expansion scale and zero suppression to allow sufficiently accurate measurements despite the small overall spectral change.

In order to avoid the interference of oxidation, the solutions of the reactants were saturated with nitrogen before mixing, and a nitrogen atmosphere was maintained in the cell compartment. For the protodesilylation reaction, the absence of the oxidation to ferricenium was indicated by the absence of any absorbance at 620 nm. In the protodeboronation reaction, a slight absorbance appeared at 620 nm only in later stages of the reaction (say beyond 75%). The wavelength (440 nm) was chosen in such a way as to keep the molar absorptivity of the ferricenium ion to a minimum. Furthermore, the absorbance data were treated by Mangelsdorf's method which neglects the infinity time absorbances.[4]

Table II
Rate Constants for the Protodesilylation and Protodeboronation of Some Ferrocene and Benzene Derivatives

Compound	Temp, °C	k, sec^{-1}	k/k_0[a]	Ref
$PhB(OH)_2$	40.0	5.0×10^{-10} [b]	1	5
$(p\text{-}MeOC_6H_4)B(OH)_2$	40.0	1.35×10^{-5} [c]	2.7×10^4	7
$Fe(C_5H_5)C_5H_4B(OH)_2$ (I)	40.0	3.5×10^{-3} [d]	7×10^6	This work
$PhSiMe_3$	51.2	3.7×10^{-8} [e]	1	6
$(p\text{-}MeOC_6H_4)SiMe_3$	50.1	3.5×10^{-5} [f]	9.5×10^2	3
$Fe(C_5H_5)C_5H_4SiMe_3$ (II)	55.2	6.12×10^{-3} [f]	1.7×10^5	This work

[a] Rate relative to the reference compound, $PhB(OH)_2$ or $PhSiMe_3$. [b] Value extrapolated at aqueous 20.1% H_2SO_4. [c] In aqueous 20.1% H_2SO_4. [d] In 20% H_2SO_4–(1:2 v/v) H_2O–EtOH mixture. [e] In 0.126 M $HClO_4$(2:5 v/v)H_2O–MeOH mixture. [f] In 0.12 M HCl–(1:4 v/v) H_2O–MeOH mixture.

ton in only 4 min in 1 M hydrochloric acid in 1:4 v/v water–methanol solvent, at 50°. While this reaction occurred an absorbance decrease was observed also in this case. The kinetics were studied by essentially the same method as were used in the case of boric acid.

As expected,[5,6] both reactions were found to be acid catalyzed. Typical data are shown in Table I.

In protodesilylation, where mild acid conditions were used, the rate constant was found to depend linearly on the HCl concentration. Similarly, using the H_0 function for aqueous H_2SO_4, log k for protodeboronation was found to correlate linearly with H_0, with a slope close to unity.

The rate constants in a given concentration range are reported in Table II together with literature data for benzene derivatives under comparable experimental conditions. The two reactions provide a consistent picture for the reactivity level of the ferrocene substrate. The latter is more reactive than the benzene analog by factors of 1.7×10^5 (protodesilylation) and 7.0×10^6 (protodeboronation). Unlike Marr and Webster's results for the protodesilylation reaction, the ferrocene substrate is even much more reactive than the p-methoxybenzene analog, the factors being in such case 9.5×10^2 (protodesilylation) and 2.7×10^4 (protodeboronation). Protodeboronation appears to be quite significantly more selective than protodesilylation.

Electrophilic ring substitutions at the ferrocene system have been suggested to occur either by a direct attack of the reagent on the ring[8] or through a preliminary iron–electrophile interaction.[9,10] The finding that protodesilylation occurs at mild acid concentrations is in contrast with the latter hypothesis for this reaction. Recent determinations of iron protonation equilibria of ferrocene derivatives[11] allow us to calculate the concentration of the iron-protonated species as exceedingly small, *i.e.*, in the order of 10^{-10} M, which makes any metal participation to speed up the reaction rate quite unlikely. The nonparticipation of the iron atom may be general for ring substitutions involving hydrogen as the electrophilic reagent; H–D exchange studies[11] are indeed in agreement with this view.

Registry No.—I, 12152-94-2; II, 12215-68-8.

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Synthesis of 6,13-Dimethyldibenz[*a*,*h*]anthracene[1]

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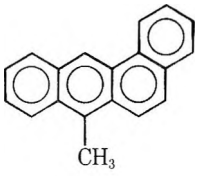
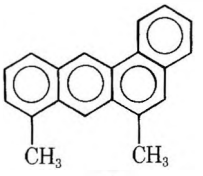
According to a hypothesis about the carcinogenic activity of benz[*a*]anthracene derivatives, the 7 position represents the main site for metabolic deactivation of members of this series.[3] The metabolic deactivation (with respect to carcinogenic activity) may be blocked by two methods: (1) substitution of a methyl group at position 7[3] and (2) substitution of methyl groups at positions 6 and 8.[4] The compounds produced by these changes, 7-methylbenz[*a*]anthracene (**1**), and 6,8-dimethylbenz[*a*]anthracene (**2**), are highly carcinogenic, presumably because the deactivation site is blocked whereas the site (position 5) at which metabolism leading to cancer occurs[3] is available for attack.



1



2

The compound dibenz[*a*,*h*]anthracene (**3**) is carcinogenic[5] and bears a structural resemblance to benz[*a*]anthracene. We were interested to see if the carcinogenic activity of **3** could be enhanced by substitution of methyl groups at positions 6 and 13 as in the case of **2**. In this paper we describe the synthesis of 6,13-dimethyldibenz[*a*,*h*]anthracene (**4**) by the route shown in Scheme I.

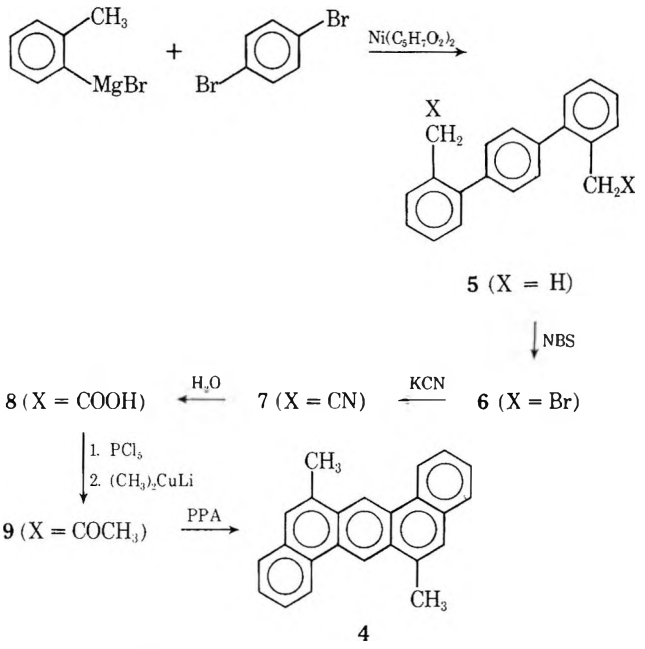
That the structure of **4** is that of a dimethyldibenz[*a*,*h*]anthracene, rather than the alternate possibility, a dimethylpicene, is indicated by the uv absorption spectrum (see Experimental Section).

Experimental Section

Generalizations. All melting and boiling points are uncorrected. Melting points were taken on a Thomas-Hoover apparatus. All compounds marked with an asterisk had ir and nmr spectra, elemental analyses (by the Galbraith Laboratories, Inc., Knoxville, Tenn., within ±0.3% of the theoretical values), and mass spectra (taken by Mr. C. R. Weisenberger on an MS-902 mass spectrometer) consistent with the assigned structures.

2,2″-Dimethyl-*p*-terphenyl (5). The Grignard reagent prepared in 1.2 l. of ether from 2.4 g of sublimed magnesium, 160 g of o-bromotoluene, and 2 ml of ethylene dibromide[6] was cooled to 0–5° by an ice bath and 1.0 g of nickel acetylacetonate[7] was added with stirring. A solution of 82.6 g of 1,4-dibromobenzene in 650 ml of dry ether was added during 3 hr under nitrogen. Two further additions of nickel acetylacetonate (0.5 g each) were made midway and at the conclusion of the addition of the dibromide.[8] After being held at reflux for 42 hr, the reaction mixture was worked up in a conventional way. The entire reaction product was distilled at 1 mm to remove unchanged *p*-dibromobenzene, bp 110–120°. The residue was crystallized from ethanol to yield 56.0 g (62%) of **5**, mp 137–140°, suitable for further use. A pure sample,[9] mp 142–143°, was obtained by recrystallization from ethanol–benzene.

Scheme I



2,2″-Bis(bromomethyl)-*p*-terphenyl* (6). A mixture of 6.95 g (0.025 mol) of **5**, 9.75 g (0.05 mol) of *N*-bromosuccinimide, and 0.3 g of benzoyl peroxide in 400 ml of carbon tetrachloride was refluxed for 30 min. After cooling, the solid was removed by filtration and the solvent evaporated from the filtrate under reduced pressure. The residue (10.2 g) was suitable for use in the next step. A sample, mp 179.5–181.0°, was obtained by recrystallization from benzene. The crude dibromide should be used soon after it is made as on standing decomposition sets in.

2,2″-Bis(cyanomethyl)-*p*-terphenyl* (7). A mixture of 10.2 g of crude **6**, 10 g of potassium cyanide, 20 ml of water, 250 ml of 2-methoxyethanol, and 150 ml of ethanol was refluxed for 20 hr. After cooling, 350 ml of water was added. After washing with water and drying the crude precipitate, 6.55 g (85% calculated on **5**), mp 228–231°, was suitable for further work. A pure sample of **7**, mp 235–237°, was obtained by recrystallization from chloroform.

2,2″-Bis(carboxymethyl)-*p*-terphenyl* (8). A solution of 24 g of crude **7** and 25 g of potassium hydroxide in 350 ml of ethylene glycol and 500 ml of water was refluxed for 20 hr. The crude acidic material obtained by acidification of the filtered (through Celite) reaction mixture weighed 23.5 g (85%) and melted at 264–268°. The analytical sample, mp 275–277°, was obtained after recrystallizations from acetic acid.

2,2″-Bis(acetonyl)-*p*-terphenyl* (9). To a stirred suspension

Table I
Ultraviolet Absorption Spectra

Compd	Uv spectra, λ_{max}, nm (log ϵ)							
10[a,b]		277 (4.63)	297 (5.20)	305 sh (4.40)	320 (4.30)	333 (4.23)	349 (4.18)	
11[a,b]		285 (4.58)	296 (4.88)	308 (4.95)	324 (4.02)	336 (4.06)	353 (4.12)	370 (4.12)
4[c]	257 (4.71)	282 (4.64)	293 (4.98)	306 (5.20)	325 (4.25)	339 (4.16)	354 (3.98)	
12[b,c]	257 (4.71)	275 (4.85)	286 (5.03)	303 (4.76)	313 (4.30)	328 (4.36)	357 (2.97)	376 (2.97)

[a] EtOH as solvent. [b] Reference 15. [c] Chloroform as solvent.

of 3.46 g of crude **8** in 500 ml of dry CH_2Cl_2 was added 4.17 g of phosphorus pentachloride at room temperature. A clear solution resulted in about 10 min. After 1 hr, the volatile material was removed under reduced pressure and a slurry of the crude acid chloride in 500 ml of dry ether was added to a threefold excess of $(CH_3)_2CuLi$ reagent[10] at −78°.[11] After 30 min, aqueous ammonium chloride was added and the neutral fraction of the reaction products was crystallized from aqueous ethanol to yield 2.54 g (74%) of **9**, mp 147–149°. The analytical sample, mp 149–151°, was obtained by recrystallization from absolute ethanol.

6,13-Dimethyldibenz[*a,h*]anthracene* (4). A well-stirred mixture of 1.0 g of **9** and 30 g of 115% polyphosphoric acid[12] was held at 160° for 30 min and then poured on ice. The hydrocarbon was extracted with chloroform and crystallized from chloroform–ethanol to yield 0.82 g (92%) of **4**: mp 273–274°, nmr ($CHCl_3$, TMS) δ 2.81 (s, 6, Ar CH_3).[13] An attempt to oxidize **4** with sodium dichromate in acetic acid[14] yielded a mixture of products. The red 2,4,7-trinitrofluorenone derivative[1] of **4** melted at 282–284° after one recrystallization from benzene. The uv spectrum of **4** in $CHCl_3$ is recorded in Table I along with spectra[15] of dibenz[*a,h*]anthracene (**10**), 7,14-dimethyldibenz[*a,h*]anthracene (**11**), and picene (**12**).

Registry No.—**4**, 39179-15-2; **4** 2,4,7-trinitrofluorenone derivative, 39179-14-1; **5**, 53092-64-1; **6**, 53092-65-2; **7**, 53092-66-3; **8**, 53092-67-4; **9**, 53092-68-5; **10**, 53-70-3; **11**, 35335-07-0; **12**, 213-46-7; *p*-dibromobenzene, 106-37-6; *N*-bromosuccinimide, 128-08-5.

References and Notes

(1) This work was supported by Grant 5-R01 CA-07394 from the National Cancer Institute, U. S. Public Health Service.
(2) Postdoctoral Research Associate.
(3) See M. S. Newman and R. F. Cunico, *J. Med. Chem.*, **15**, 323 (1972), for a discussion and references.
(4) M. S. Newman and S. Blum, *J. Med. Chem.*, **7**, 466 (1964).
(5) J. L. Hartwell, "Survey of Compounds Which Have Been Tested for Carcinogenic Activity," U.S. Public Health Service Publication No. 149, U.S. Government Printing Office, Washington D.C., 1951.
(6) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).
(7) Used as obtained from Research Organic/Inorganic Chemical Corp., Belleville, N.J.
(8) This procedure is based on work of R. J. P. Corrin and J. P. Masse, *J. Chem. Soc., Chem. Commun.*, 144 (1972).
(9) A melting point of 146° was reported by H. O. Wirth, K. H. Gönner, R. Stück, and W. Kern, *Makromol. Chem.*, **63**, 30 (1963).
(10) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).
(11) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 4647 (1970).
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(13) The nmr equipment was purchased in part with funds from a departmental grant from the National Science Foundation.
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Attempted Synthesis of *cis*-Cyclobutene-3,4-dicarboxaldehyde

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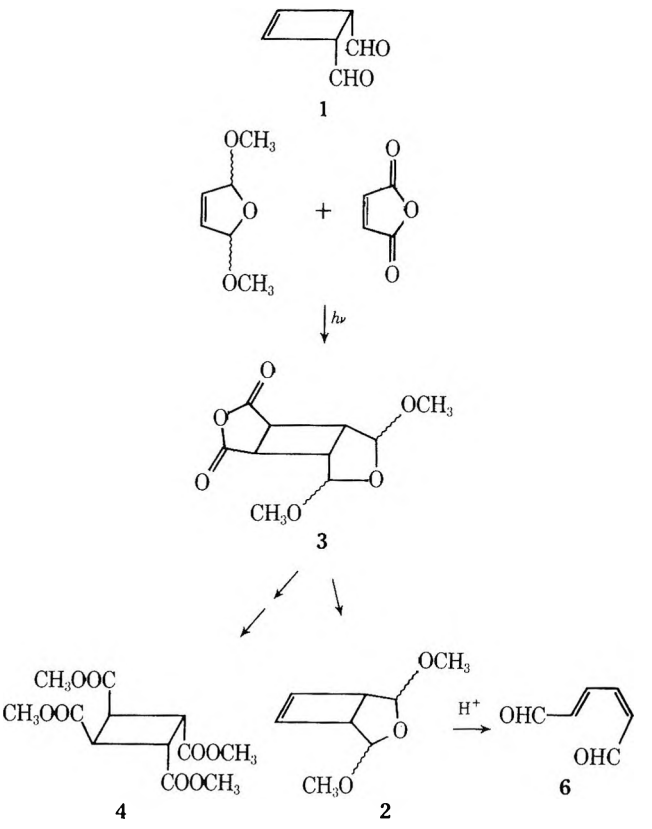
In connection with work aimed toward the synthesis of some polycyclic systems containing a fused cyclobutene ring, the preparation of the unknown *cis*-cyclobutene-3,4-dicarboxaldehyde (**1**) for use as a synethetic intermediate appeared attractive.

Consideration of potential routes for preparing substituted succindialdehydes led to the selection of the cyclic acetal **2** as a possible convenient precursor to **1**.[1] Accordingly, the preparation of **2** was carried out as outlined in Scheme I.

Benzophenone-sensitized photocycloaddition[3] of maleic anhydride to 2,5-dimethoxy-2,5-dihydrofuran (commercially available isomeric mixture) gave adduct **3** in 40% yield. The structure of **3** followed from its correct elemental analysis, mass spectrum, and the nmr spectrum, which clearly showed the correct number and kinds of hydrogens (see Experimental Section). Furthermore, dilute hydrochloric acid hydrolysis of **3** followed by potassium permanganate oxidation gave a tetracarboxylic acid characterized as its tetramethyl ester **4**, which was identical with an authentic sample[4] of *cis,trans,cis*-1,2,3,4-tetracarbomethoxycyclobutane. These combined results clearly establish the gross structure of **3**.[5]

Scheme I



Dissolution of **3** in water containing triethylamine followed by electrolytic decarboxylation[6] in pyridine gave the desired cyclobutene **2** in 10% yield after evaporative distillation. Elemental analysis and mass spectral data were completely consistent with the assigned structure, and the nmr spectrum showed two olefinic protons as a triplet (J = 0.6 Hz), a characteristic feature of bicyclo[3.2.0]hept-6-enes.[7]

Unfortunately, **2** did not prove a ready precursor to **1**. Mild hydrolysis of **2** with aqueous mineral acid led to the formation of *cis,trans*-muconic dialdehyde (**6**)[8] in high yield. Hydrolysis of **2** was then examined using a broad spectrum of acidic reagents.

In all cases, only starting acetal **2** and/or dialdehyde **6** or total decomposition was observed. Some results are summarized in Table I.

In order to examine the possibility that **6** could be arising *via* acid-catalyzed cleavage of the central bond in **2**, monocyclic acetal **5** was prepared (Scheme II) and its hydrolysis examined.

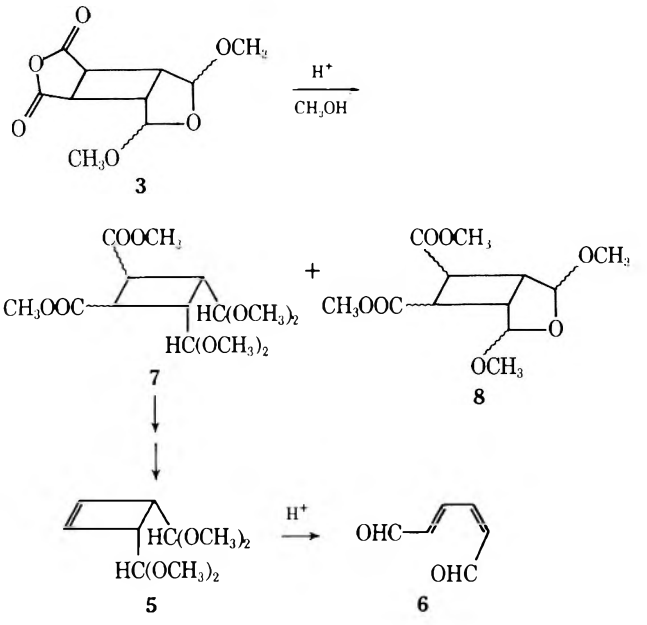
Boiling a solution of **3** in methanol containing a trace of sulfuric acid gave a mixture of **7** and **8** (90:10), from which an oil more enriched in **7** could be obtained. Basic hydrolysis of **7** (aqueous sodium hydroxide) followed, without isolation, by electrolytic decarboxylation[6] gave **5** as a colorless liquid. Analytical and spectral data were clearly in accord

Table I
Results of Treatment of Acetal 2 with Acidic Reagents

Expt	Acid reagent	Solvent	Temp, °C	Time	Product(s) (ratio)[a]
1	$MgSO_4$[b]	Wet $CHCl_3$	25	24 hr	**2**
2	1% acetic acid	H_2O	60–70	2 min	**2**
3	1% acetic acid	H_2O	90	5 min	**2** + **6**[c] (40:60)
4	Amberlite IR-120 (H^+) ion-exchange resin	H_2O	60–70	2 min	**2** + **6** (70:30)
5	0.1 *N* HCl	H_2O	70–80	3 min	**6**[c]
6	0.1 *N* $HClO_4$	H_2O	60–70	90 sec	**6**
7	0.1 *N* $HClO_4$	H_2O	25	18.5 hr	**2** + **6**(40:60)
8	BBr_3	CH_2Cl_2	−78	10 min	Decomposition
9	BBr_3	CH_2Cl_2	−60	5 min	Decomposition

[a] By nmr analysis. [b] J. J. Brown, R. H. Lenhard, and S. Bernstein, *J. Amer. Chem. Soc.*, **86**, 2183 (1964). [c] Some isomerization of *cis,trans*-muconic dialdehyde (**6**) to the trans,trans-isomer was observed.[8]

Scheme II



with the desired structure[9] (see Experimental Section). Unfortunately, mild acid hydrolysis of **5** gave again *cis,trans*-muconic dialdehyde (**6**) and not the desired dialdehyde **1**.

The factor(s) responsible for the remarkably facile and stereospecific ring opening observed on hydrolysis of acetals **2** and **5** is of interest. One explanation involves the intermediate formation of the desired *cis*-cyclobutenedicarboxaldehyde (**1**) followed by a rapid acid-catalyzed conrotatary[10] ring opening leading to the observed *cis,trans*-diene **6**. This is supported by the reported mild (acid-catalyzed?) thermal stereospecific ring opening of the structurally related tetramethyl *cis*-diacetoxycyclobutene.[11]

Of course, the ring opening of **2** and **5** need not proceed through the intermediacy of **1**. Indeed, as alternative explanation suggests that the observed stereospecific ring opening could be an example of a solvolytic electrocyclic reaction.[12] The developing positive charge on carbon formed during protonation of the acetal oxygen(s) in **2** and **5** stabilizes, and in turn is stabilized by, the developing π orbitals involved in the electrocyclic ring opening.[13] This phenomenon has recently been suggested as occurring in certain solvolytic Cope rearrangements.[12]

Experimental Section[14]

Photocycloaddition of Maleic Anhydride and 2,5-Dimethoxy-2,5-dihydrofuran. Preparation of 3. A solution of 26 g of distilled 2,5-dimethoxy-2,5-dihydrofuran (Eastman), 10 g of maleic anhydride, and 5 g of benzophenone in 270 ml of acetonitrile was irradiated (Hanovia 450-W lamp, Pyrex filter) under nitrogen for 48 hr. The solvent was removed under reduced pressure and the residue was treated with 250 ml of ethyl ether. The mixture was rapidly stirred for several hours, after which time the solid was collected and washed with ether giving 10 g (44%) of powdery crude product. A sample recrystallized two times from butyl acetate had mp 231–233°: ir (KBr) 5.40 and 5.58 μ (anhydride); mass spectrum *m/e* 227 (M − H),[15] 197 (M − OCH_3); nmr (DMSO-d_6, 90 MHz) δ 5.26 (s, 2 H), 3.25 (s overlapping m, 8 H), 3.04 (m, 2 H); upon standing in solution new absorptions appear, δ 5.04 (s) and 2.93 (m), at the expense of the original absorptions, indicating an isomerization phenomenon.

Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.6; H, 5.30. Found: C, 52.8; H, 5.6.

2,4-Dimethoxy-3-oxabicyclo[3.2.0]hept-6-ene (2). A sample of 5.0 g of crude **3** was dissolved with warming in a mixture of 7 ml of triethylamine and 50 ml of water. This solution was added to 350 ml of pyridine in a water-jacketed electrolysis cell. The mixture was stirred and electrolyzed (platinum gauze electrodes) with an initial current of 0.8 A for 4–5 hr, after which time no additional current drop was noted. About 250 ml of pyridine was removed from the dark reaction solution by distillation at about 30 mm (pot temperature 50–55°). The concentrate was diluted with 400 ml of 5% aqueous nitric acid (mixture not acidic) and the solution was continuously extracted with ether overnight. The ether extracts were washed with 5% nitric acid until the washings were acidic, and then were washed with aqueous sodium bicarbonate solution. The dried organic layer was concentrated by distillation. The residue was evaporatively distilled (30 mm, pot temperature to 100°) to give 350 mg (10%) of **2** as a colorless to pale yellow liquid: mass spectrum *m/e* 155 (M − H)[15] 125 (M − OCH_3); nmr ($CDCl_3$, 90 MHz) δ 6.10 (t, 2 H, J = 0.6 Hz), 4.92 (s, 2 H), 3.45 (s overlapping multiplet, 8 H).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.5; H, 7.75. Found: C, 61.8; H, 7.9.

Acid Hydrolysis of 2. A mixture of 50 mg of **2** in 1 ml of 0.1 *N* $HClO_4$ was heated on a steam bath with shaking for 90 sec; the bright yellow solution was quickly cooled in ice and neutralized with sodium bicarbonate. The solution was extracted with 0.5 ml of $CDCl_3$. Nmr of the extracts showed no starting material and only absorptions attributable to *cis,trans*-muconic dialdehyde.[16] The $CDCl_3$ extract was dried and concentrated to an orange solid, mp 45–55°, which showed an ir spectrum identical with the published spectrum of *cis,trans*-muconic dialdehyde.[8] Recrystallized from ligroin, the material had mp 53–55° (lit.[8] mp 59°).

***cis*-Cyclobutene-3,4-diearboxaldehyde bis(dimethyl acetal) (5).** A slurry of 2.28 g of **3** in 75 ml of methanol containing 1 drop of concentrated sulfuric acid was refluxed for 2 hr. The acid was neutralized with a small amount of solid sodium methoxide and the methanol removed under reduced pressure. The residue was dissolved in ether, filtered to remove a small amount of insoluble material, and the solvent was removed under reduced pressure. Upon standing, the oily residue partially recrystallized. A small amount of ether was added and the solid material was collected and washed with ether to give **8**, mp 140–144°: mass spectrum *m/e* 273 (M − H),[15] 243 (M − OCH_3); nmr ($CDCl_3$, 60 MHz) δ 4.98 (s, 2 H), 3.68 (s, 6 H), 3.41 (s, 6 H), 3.16 (m, 4 H). The ether filtrate was concentrated to an oil, which was evaporatively distilled (0.02 mm, pot temperature 150°) giving **7** as a viscous, colorless oil contaminated with a small amount of **8**. Mass spectrum *m/e* 305 (M − CH_3), 289 (M − OCH_3),[15] nmr ($CDCl_3$, 60 MHz) δ 4.55 (m, 2 H) 3.66 (s, 6 H), singlets at 3.34 and 3.30 obscuring multiplets (16 H).

A crude sample of 7 was refluxed 2 hr with aqueous sodium hydroxide. The resulting solution was stirred at room temperature with excess Amberlite IR-120 (H^+) ion-exchange resin and filtered. The resulting aqueous solution of bis(carboxylic acid) was neutralized with triethylamine and electrolyzed in pyridine exactly as described for the preparation of 2 above. Work-up as previously described and purification by preparative gas chromatography (5 ft × ¼ in., 5% SE-30 on Anakron ABS at 100°) gave 5 (5% overall from 3) as a colorless liquid: mass spectrum *m/e* 171 ($M - OCH_3$),[15] 170 ($M - CH_3OH$); nmr ($CDCl_3$, 90 MHz) δ 6.12 (slightly broadened s, 2 H), 4.53 and 3.23 (4 H, AA'XX'), 3.39 (s, 6 H), 3.36 (s, 6 H).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.4; H, 8.97. Found: C, 59.2; H, 9.1.

Acknowledgment. The author wishes to thank Mr. D. P. Maier and Dr. T. H. Regan of these laboratories for assistance in obtaining and interpreting mass spectral and nmr data, respectively.

Registry No.—**2**, 53042-82-3; **3**, 53042-83-4; **5**, 53042-84-5; **6**, 53042-85-6; **7**, 53042-36-7; **8**, 53042-87-8; maleic anhydride, 108-31-6; 2,5-dimethoxy-2.5-dihydrofuran, 332-77-4.

References and Notes

(1) This route is rendered even more attractive when one recalls that an analogous procedure represents a convenient method for the preparation of *cis*-cyclopropanedicarboxaldehyde.[2]
(2) G. Maier and T. Sayrac, *Chem. Ber.*, **101**, 1354 (1968).
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(5) Unfortunately, of course, this degradation study does not unequivocally establish the stereochemistry of **3** owing to the possible fortuitous isomerization of an all-cis structure during the acid hydrolysis. Although the gross stereochemistry of **3** was presumed trans, this question, in addition to the complicated question concerning the additional stereochemistry in **3** with respect to the dimethoxytetrahydrofuran ring, was not pursued further.
(6) P. Radlick, R. Klem, S. Spurlock, J. J. Sims, E. E. van Tamelen, and T. Whitesides, *Tetrahedron Lett.*, 5117 (1968); H. H. Westberg and H. J. Dauben, Jr., *ibid.*, 5123 (1968).
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(8) M. Nakajima, I. Tomida, and S. Takei, *Chem. Ber.*, **92**, 163 (1959).
(9) Although the cis stereochemistry of **5** was not unequivocally established, the formation of *cis,trans*-muconic dialdehyde as the sole hydrolysis product substantiates this formulation.[10]
(10) R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Verlag Chemie, Academic Press, New York, N.Y., 1970.
(11) G. Maier and M. Wiessler, *Tetrahedron Lett.*, 4987 (1969).
(12) R. Breslow and J. M. Hoffman, Jr., *J. Amer. Chem. Soc.*, **94**, 2111 (1972).
(13) A similar mechanism can be envisaged for the above-postulated acid-catalyzed ring opening of **1** and of the tetramethyl-*cis*-diacetoxycyclobutene.
(14) Melting points are uncorrected. Nmr spectra were determined on Varian T-60, Varian A-60, and Bruker HX-90 spectrometers. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Mass spectra were taken on a CEC 21-110B instrument. Gas chromatography was performed on a Varian Model 90-P instrument.
(15) Characteristic of tetrahydrofuran derivatives and acetals: H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, Chapter 6.
(16) J. A. Elvidge and P. D. Ralph, *J. Chem. Soc. C*, 387 (1966).

Reactions of Olefins with Bromine, *N*-Bromosuccinimide, and *N*-Bromoacetamide in Dimethyl Sulfoxide and Methanol

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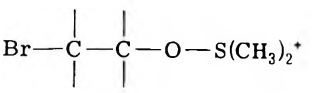
In the course of our studies on electrophilic addition of the elements of BrOH (NBS and H_2O) to olefins in dimethyl sulfoxide (DMSO), we became interested in the relative nucleophilicity of the DMSO molecule toward the intermediate bromonium ion. There are two studies in the literature which indicate that DMSO competes very favorably with other nucleophiles. In one of these studies, Dalton and coworkers[1] using isotope-labeling experiments showed that the bromonium ion is apparently opened exclusively by DMSO when an olefin is allowed to react with NBS in a mixture of DMSO and H_2O. In the other study, Torssell[2] examined the reactions of cyclohexene with $BrC(NO_2)_3$ in DMSO (with various ions present), and with Br_2 in DMSO, and observed in all cases that considerable solvent (DMSO) was incorporated. In neither case was a systematic study made of the nucleophilicity of DMSO. We proposed to do this.

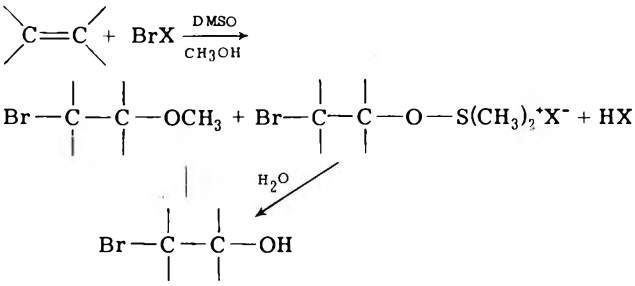
Both of these studies[1,2] provided evidence that solvent incorporation produced an intermediate sulfonium ion of the following structure



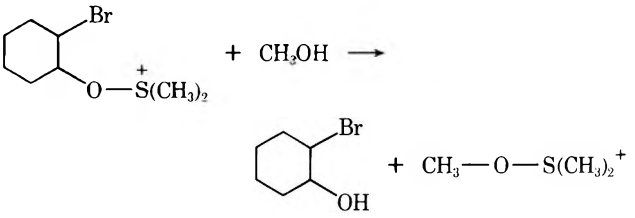
Results and Discussion

We proposed (Scheme I) to compare the nucleophilicities of DMSO and methanol by brominating olefins in DMSO–CH_3OH mixtures, and then determining the methoxy bromide/bromohydrin ratio. We envisioned that the bromohydrin would be formed by addition of the bromination product to water. During the course of this study it became apparent that under certain conditions, bromohydrin is formed directly during the bromination reaction, before water has been added. The following reaction is probably involved

Scheme I



X = bromide, succinimate, or acetamate

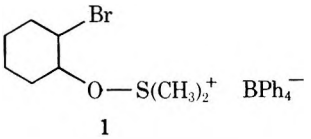


Formation of bromohydrin by reaction of the sulfonium ion with methanol is important with NBS (and probably NBA), but not with Br_2 since a reasonably high temperature is required for this reaction,[3] and a sufficiently high temperature does occur with NBS and NBA. In order for Scheme I to be valid, it was necessary to establish that no methoxy bromide was formed by reaction of the intermediate sulfonium ion with methanol. To this end, sulfonium ion (1) was synthesized as previously reported,[2] and we

Table I
Bromination of Olefins in Dimethyl Sulfoxide and Methanol

Entry	Reactants: Hal,[a] concn[d]	Reactants: Olefin, concn	Reactants: CH_3OH DMSO	Rel[g] reactivity	Products: Br,OH / Br,OCH_3	Products: Br, OCH_3[b]	Products: Br,OH[c]	Products: DiBr	Material[e] balance, %
1	NBS, 0.05	Styrene, 0.10	0.441	3.47	7.87	10.6	83.7	5.7	41.2
2	NBS, 0.10	Styrene, 0.05	0.441	3.80	8.62	8.6	74.1	17.3	66.8
3	NBA, 0.10	Styrene, 0.05	0.441	3.24	7.35	9.6	70.6	19.8	95.9
4	Br_2, 0.05	Styrene, 0.10	0.441	2.39	5.43	9.3	50.6	40.0	88.6
5	NBS, 0.09	Styrene, 0.045	1.77	2.15	1.22	37.0	45.3	17.7	101
6	NBS, 0.08	Styrene, 0.04	7.00	1.78	0.254	70.3	17.9	6.9	98.9
7	NBS, 0.05	Cyclohexene, 0.10	0.441	6.79	15.4	5.5	84.4	10.1	17.6
8	NBS, 0.10	Cyclohexene, 0.05	0.441	6.04	13.7	4.3	59.0	36.7	47.8
9	NBA, 0.10	Cyclohexene, 0.05	0.441	5.34	12.1	4.2	51.1	44.7	108
10	Br_2, 0.05	Cyclohexene, 0.10	0.441	2.69	6.10	3.9	23.7	77.3	103
11	NBS, 0.09	Cyclohexene, 0.045	1.00	3.36	3.36	14.7	49.4	35.9	56.0
12	Br_2, 0.45	Cyclohexene, 0.09	1.00	1.96	1.96	10.7	21.0	68.3	102
13[f]	Br_2, 0.45	Cyclohexene, 0.09	1.00	2.19	2.19	10.3	22.6	67.1	104
14	NBS, 0.09	Cyclohexene, 0.045	1.77	2.78	1.57	23.5	36.9	39.6	88.3
15	Br_2, 0.45	Cyclohexene, 0.09	1.77	1.82	1.03	17.9	18.4	63.7	113
16	NBS, 0.08	Cycloxene, 0.04	7.00	1.77	0.253	63.9	16.2	19.9	91.2

[a] Hal = halogenating agent. [b] Br,OCH_3 = methoxy bromide. [c] Br,OH = bromohydrin. [d] Concentrations are expressed as mole fractions. Ratios are computed on a molar basis. [e] Material balances are based on the olefin or halogenating agent (whichever is present in smallest amount). [f] Bromination was done from 45 to 50°. [g] The relative reactivity was obtained from the following expression: [(Br,OH/Br,OCH_3)-(CH_3OH/DMSO)].



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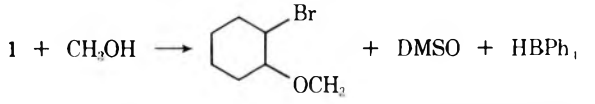
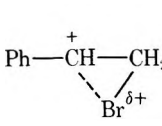
confirmed that the following reaction does not occur under our reaction conditions.

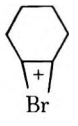


Furthermore, vpc analysis of a reaction mixture (resulting from olefin, solvents, and halogenating agent) indicated that the same amount of methoxy bromide was present before and after hydrolysis.

Table I contains data from the reactions of cyclohexene and styrene with NBS, NBA, and Br_2 in which the ratios of brominating agent to olefin and DMSO to CH_3OH are varied systematically. Under these conditions DMSO is observed to be *ca.* two to seven times more nucleophilic than CH_3OH. Although the relative reactivities do not vary greatly, some interesting observation can be made from these data. For example, the relative reactivities toward the intermediate bromonium ions (entries 4 and 10) when Br_2 is the electrophile are nearly identical, whereas with NBS and NBA (which react similarly, entries 2, 3 and 8, 9) the relative reactivity of DMSO increases (compared to Br_2) *ca.* 1.3 times with styrene and 2.2 times with cyclohexene.[4] This result suggests that NBS and NBA involve distinctly different brominating species than Br_2 and that the former do not brominate (at least primarily) *via* molecular Br_2.[5,6] An explanation for this difference in reactivity between these brominating agents may involve considerations of the intermediate ion pairs that result from the reactions of the brominating agents with the olefins. We anticipate that Br_2 would react *via* the bromonium ions (with bromide as the anion in the ion pair) shown below for styrene[7] (**2**) and cyclohexene (**3**), and that these reactive intermediates would show essentially the same relative reactivities toward DMSO and CH_3OH. However, since the ion pairs from NBS and NBA (succinimate and acetamate anions) would

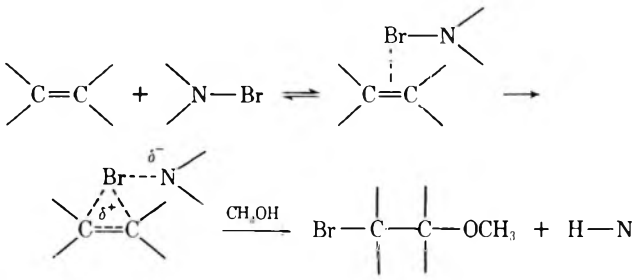


2



3

be of considerably higher energy than the ion pairs from Br_2, the former may not produce ion pairs at all, but may react with the nucleophile *via* a complex, as



The complexes would be less reactive than the bromonium ion and, therefore, the greater nucleophilicity of DMSO would be apparent.

The data also indicate that DMSO (with NBS and NBA) shows a lower relative reactivity with the complex from styrene than from cyclohexene. We interpret this to mean that greater carbonium ion character develops in the complex with styrene (because of the stability of the benzyl ration), and that the weaker nucleophile CH_3OH competes more favorably in this case than with the complex from cyclohexene.

Experimental Section

Reaction Conditions. To a well-stirred solution of the appropriate amount of DMSO, CH_3OH, and olefin (volume of the reaction *ca.* 60 ml) at 10° was added NBS (or NBA) as rapidly as possible with a spatula. After a brief induction period the temperature rose from 20 to 30°; stirring was continued for 15 min. The reaction was worked up by pouring the product into water and extracting it with ether.

Brominations with bromine were done in the same way with the exception that the bromine was added dropwise and the temperature was maintained at the indicated levels.

Vpc Analysis Conditions. The styrene reaction mixtures were

analyzed on a 6 ft × 0.125 in. steel column packed with 2.5% SE-30 on 80–100 mesh DMCS Chromosorb with an oven temperature of 89° and a flow rate of 56 ml/min. The retention times (min) of the products were determined as follows: 1-methoxy-1-phenyl-2-bromoethane (8.5), 1-phenyl-2-bromoethanol (13.0), and 1,2-dibromo-1-phenylethane (15.7).

The cyclohexene reaction products were analyzed on a 6 ft × 0.125 in. steel column packed with 2.5% DNP at 75° and a flow rate of 60 ml/min. The retention times (min) of the products were determined as follows: *trans*-1-bromo-2-methoxycyclohexane (6.3), *trans*-2-bromocyclohexanol (8.6), and *trans*-1,2-dibromocyclohexane (13.9).

Percentages of products and material balances were determined by using *p*-dichlorobenzene as an internal standard.

Product Identification. Styrene dibromide was prepared by addition of bromine to styrene. The other products were synthesized as follows. **1-Methoxy-1-phenyl-2-bromoethane** (bp 57° (0.40 mm), lit.[8] 117–118° (15 mm), structure also confirmed by ir) and ***trans*-1-bromo-2-methoxycyclohexane** were prepared according to the procedure of Iovchev.[9] **1-Phenyl-2-bromoethanol** was synthesized (three different ways) by the procedures of Dalton, *et al.*[1] (bp 90° (0.3–0.5 mm)), Guss and Rosenthal[10] (82° (0.4 mm)), and by reduction of phenacylbromide with $NaBH_4$ (bp 84, 85° (0.4 mm)). Only the latter procedure afforded a product which was free of carbonyl absorption in its ir spectrum. ***trans*-2-Bromocyclohexanol** was synthesized as reported by Dalton, *et al.*[1] ***trans*-1-Dibromocyclohexane** was prepared by the bromination of cyclohexene in pentane (bp 47° (0.8 mm), n^{25}D 1.5497; lit.[11] bp 145–146 (100 mm), n^{25}D 1.5495).

A Summary of the Studies on the Intermediate Sulfonium Ion. The DMSO that was used in our study always contained a trace of water (as determined by vpc). We established, however, that this trace of water did not hydrolyze sulfonium ion (1) even after standing for hours. Addition of sufficient water to the mixture caused rapid conversion to the corresponding bromohydrin.

Early in this study we experienced considerable difficulty on direct vpc analysis of a DMSO–1 mixture since 1 decomposed in the injection port to produce the corresponding bromohydrin. We found that decomposition in the injection port could be avoided if the DMSO solution of 1 was mixed with THF before injection. Apparently THF caused instant volatilization in the injection port and did not permit the sulfonium salt to fall on the hot injection port and decompose.

We observed that methanol (in DMSO) does not react with 1 at 10°, however, when this mixture was heated at 50°, 1 was rapidly converted to the bromohydrin.

We confirmed that the sulfonium ion (with Br^- as the anion) is an intermediate in the bromination (Br_2) of cyclohexene in DMSO in the following manner. Vpc analysis of the reaction product resulting from the addition of Br_2 to cyclohexene in DMSO showed that no bromohydrin was present. Analysis after addition of water to this mixture indicated that bromohydrin was now present.

Stability of the Products to the Reaction Condition. We confirmed that all of the products of the bromination reactions (the bromohydrins, methoxy bromides, and dibromides) did not react further with the solvents or with each other.

Acknowledgment. Support for this work was provided by the Research Corporation and the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—NBS, 128-08-5; NBA, 79-15-2; Br_2, 7726-95-6; dimethyl sulfoxide, 67-68-5; methanol, 67-56-1; styrene, 100-42-5; cyclohexene, 110-83-8.

References and Notes

(1) D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Amer. Chem. Soc.*, **90**, 5498 (1968).
(2) K. Torssell, *Acta Chem. Scand.*, **21**, 1 (1967).
(3) Torssell[2] has shown that this reaction does take place at higher (~50°) solvent temperature. We have shown that it does not occur, or is very slow, at lower temperature (~10°).
(4) These values were obtained by averaging entries 1, 2, 3 and 7, 8, 9 and comparing the averages to the corresponding result with Br_2.
(5) Dalton, *et al.* (ref 1), question the nature of the brominating agent when NBS is used in DMSO; they conclude that Br_2 may be involved. Our results indicate that Br_2 is not the principal source of positive bromine under these conditions.
We do assume that some Br_2 is involved, however, since dibromides are formed. The Br_2 probably results from the reaction of HBr and NBS; bromination of the solvent (DMSO) by NBS may produce the HBr. We have established that the dibromides do not result from direct reaction between HBr and the intermediate sulfonium ion. Also, sodium bromide did not react with **1** in DMSO to give dibromide. We have no explanation for the fact that more dibromides are formed with cyclohexene than styrene.
(6) It occurred to us that conceivably the difference in relative reactivity ratio between Br_2 and NBS could result from decomposition of NBS to Br_2 at the higher reaction temperature (the temperature rises from *ca.* 10 to 40° during the NBS reactions), and addition of Br_2 to olefins at this higher temperature might give a higher Br,OH/Br,OCH_3 ratio. This does not seem to be the case, however, since brominations at 5–10° (entry 12) and 45–50° (entry 13) gave very similar results.
(7) We assume that bromonium ion 2 has unsymmetrical bridging between the bromine and the benzylic carbon. (See R. C. Fahey and H. J. Schneider, *J. Amer. Chem. Soc.*, **90**, 4429 (1968).)
(8) W. M. Laver and M. A. Spielmann, *J. Amer. Chem. Soc.*, **55**, 4923 (1933).
(9) A. Iovchev, *Izv. Inst. Org. Khim. Bulg. Akad. Nauk.*, **2** 67 (1965).
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(11) "Handbook of Chemistry and Physics," 51st ed, Chemical Rubber Co., Cleveland, Ohio, 1970.

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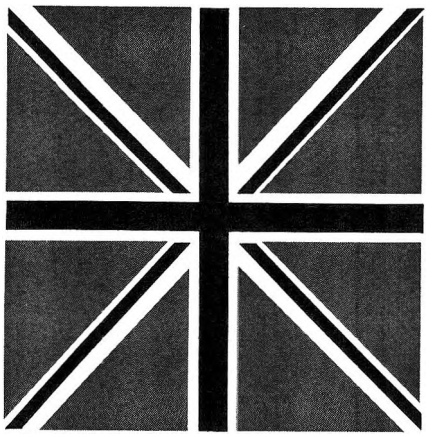

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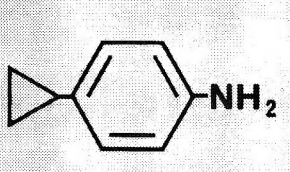

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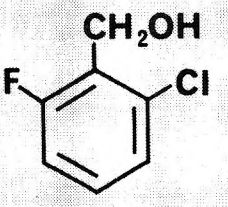

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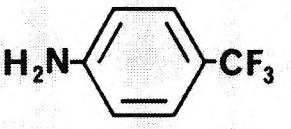

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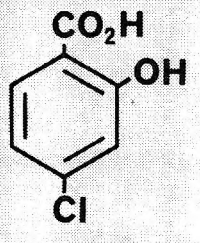

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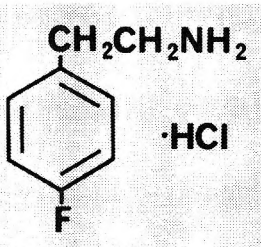

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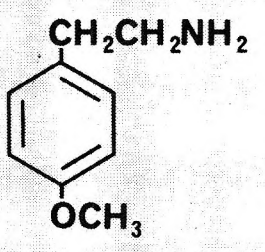

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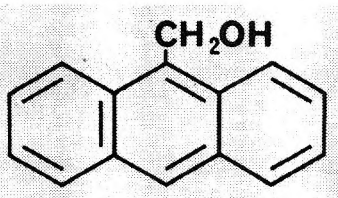

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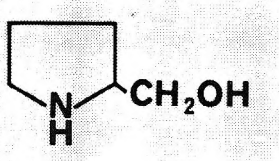

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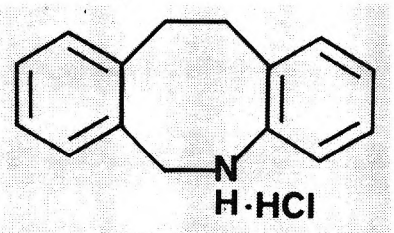

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