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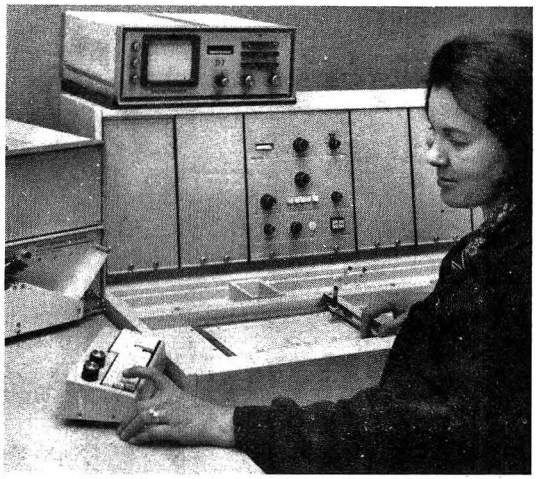

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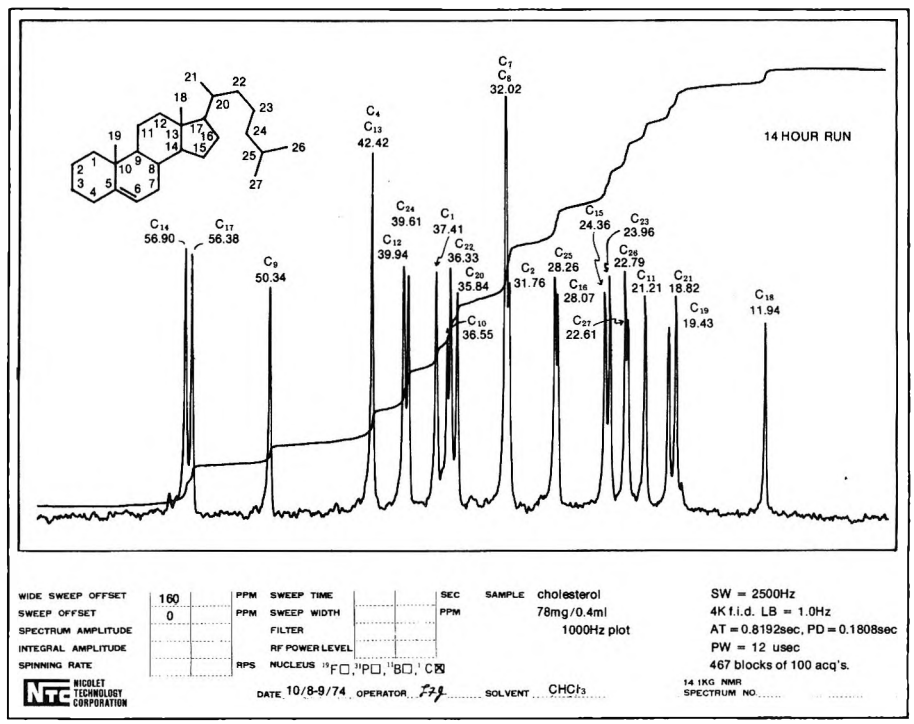

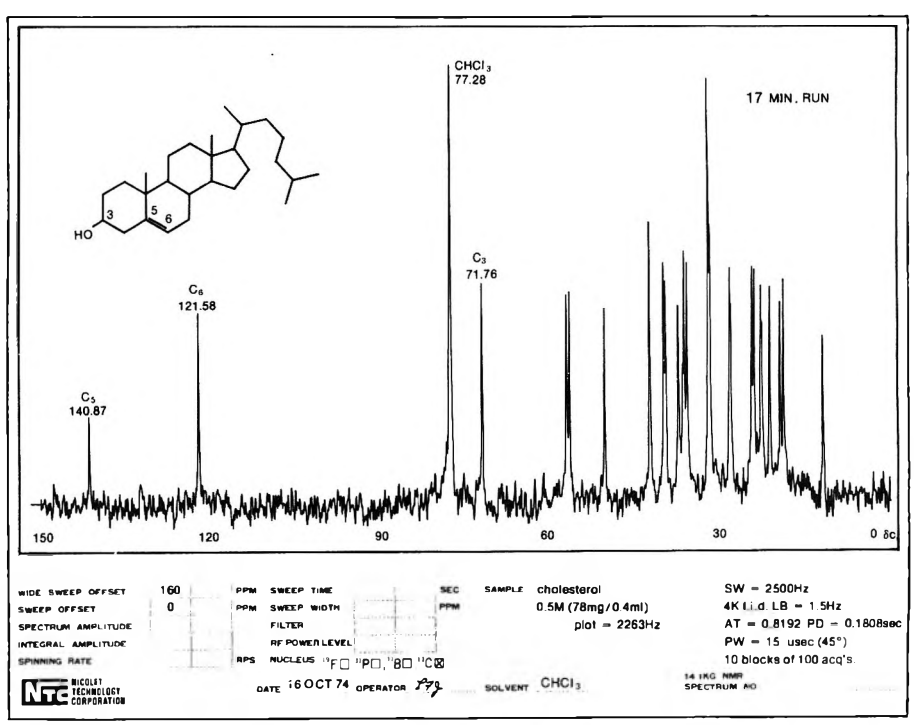

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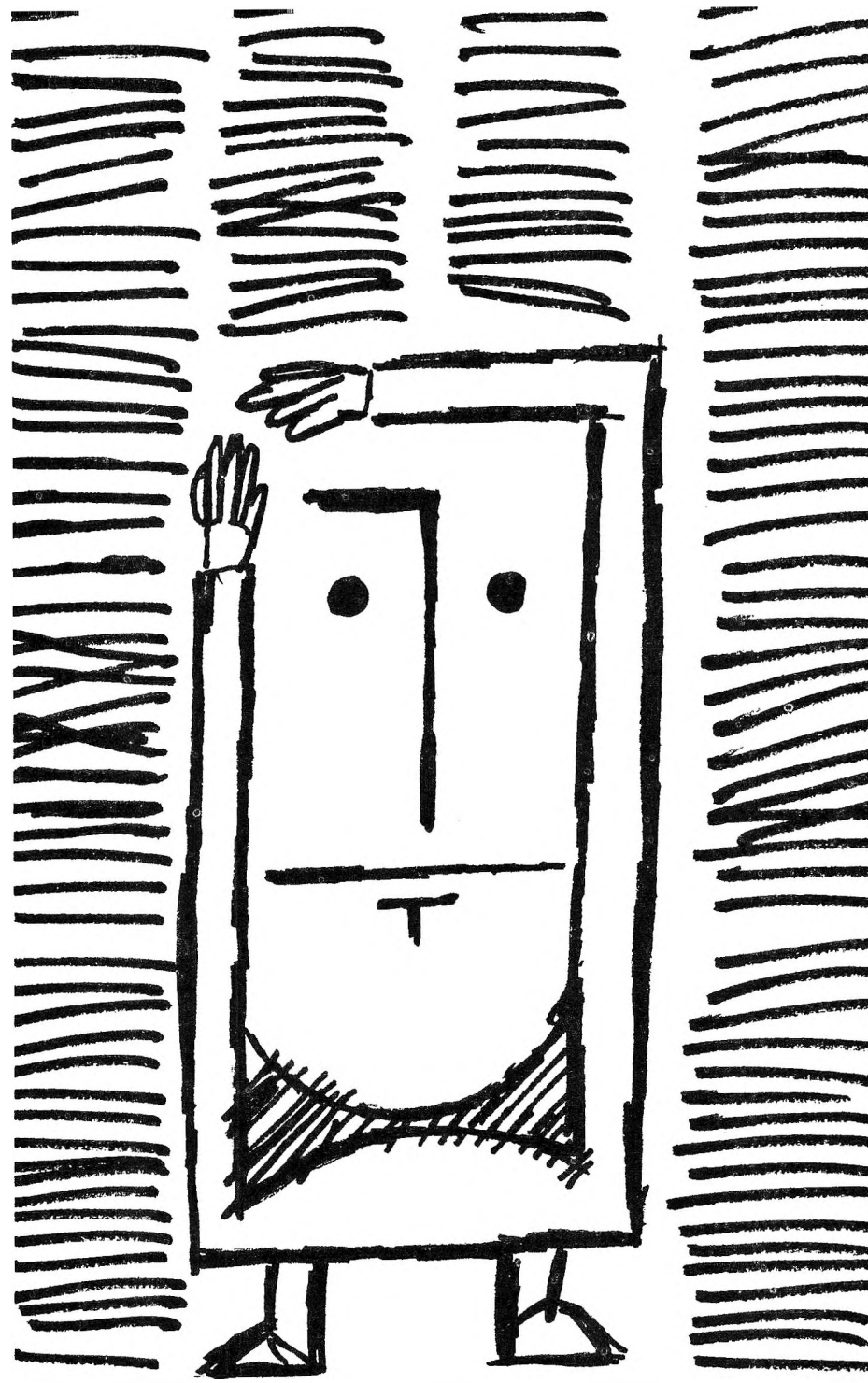

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Alkylation–Reduction of Carbonyl Systems. IV. The Convenient and Selective Synthesis of Simple and Complex Aromatic Hydrocarbons by Phenylation–Reduction of Aldehydes and Ketones

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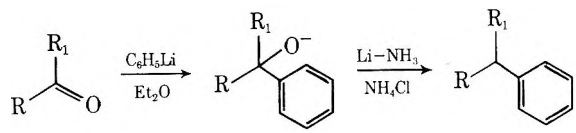
Received August 8, 1974

Simple and complex aromatic hydrocarbons are conveniently prepared from aldehydes and ketones by tandem phenylation–reduction. By this procedure benzyl alkoxides, generated *in situ* by phenylation, are reduced by lithium–ammonia–ammonium chloride to the corresponding aromatic hydrocarbons. Complex aldehydes and ketones, containing structural features or other functional groups which might not be compatible with the reaction conditions, were subjected to the phenylation–reduction sequence to explore the limits of this simple synthetic procedure as an efficient and selective synthesis of rather complex molecular structures. These structural features or functional groups included steric hindrance, terminal olefins, isolated double bonds, α,β-unsaturated carbonyl systems, an $\alpha,\beta,\gamma,\delta$-unsaturated ketone system, α,β-unsaturated aldehyde systems containing isolated double bonds, a cross-conjugated ketone, a cyclopropane ring, aromatic systems, and heterocycles.

This laboratory innovated the concept of tandem alkylation–reduction of aromatic carbonyl systems as a convenient method of preparing aromatic hydrocarbons by the lithium–ammonia reduction of benzyl alkoxides generated *in situ* by alkylation.[1] The mechanistic and selective synthetic utility of the procedure was then demonstrated for the synthesis of aromatic hydrocarbons and alcohols by the alkylation–reduction of benzylidene ketones and aldehydes.[2] Herein we report the extension of this convenient procedure for the selective synthesis of simple and complex aromatic hydrocarbons in excellent isolated yields by the phenylation–reduction of appropriate aldehydes and ketones.

The general procedure, which is carried out in the same reaction vessel and consumes only a few hours, is to generate a benzyl alkoxide in a metal–ammonia reaction vessel[3] by the addition of the aldehyde or ketone to phenyllithium, prepared *in situ* from bromobenzene and excess lithium, in ether. Ammonia is subsequently distilled into the vessel, and then the resulting dark blue mixture is cautiously quenched with ammonium chloride.[4]

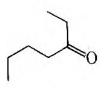
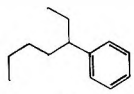
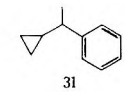
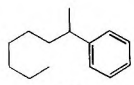
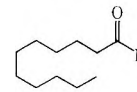
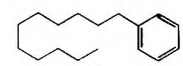
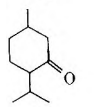
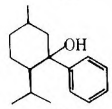
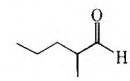
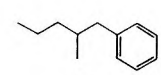
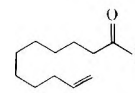
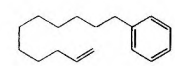
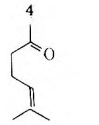
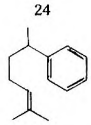
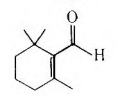
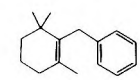
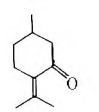
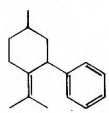
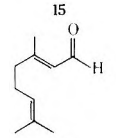
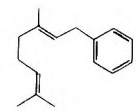
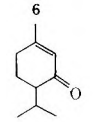
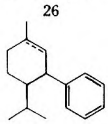
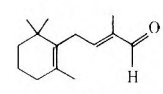
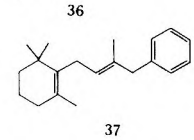
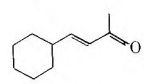
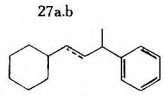
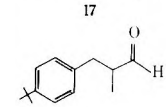
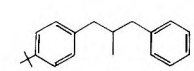
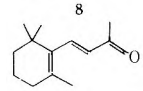
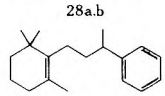
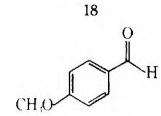
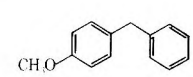
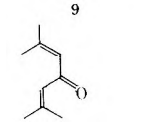
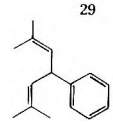
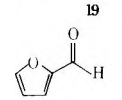
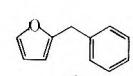


The primary objective of this study, after first demonstrating the feasibility of the procedure with simple aldehydes and ketones, was to test the method using aldehydes and ketones containing structural features or functional groups which may or may not be compatible with the conditions. By so doing, we would explore the possible limits of this simple synthetic procedure as a selective method of preparing complex aromatic hydrocarbons which might be difficult to elaborate by conventional methods.

Table I contains a listing of the aldehydes and ketones that were subjected to this procedure. The carbonyl compounds were carefully selected to include the following structural features or functional groups: steric hindrance,[5] terminal olefins,[6] isolated double bonds, α,β-unsaturated carbonyl systems, an $\alpha,\beta,\gamma,\delta$-unsaturated ketone system (a 1,3-diene system[7] after phenylation–reduction), α,β-unsaturated aldehyde systems containing isolated double bonds (one of which is a 1,4-diene system[8] after phenylation–reduction), a cross-conjugated ketone, a cyclopropane ring,[9] aromatic systems,[10] and heterocycles[9a,11]—features and groups that might interfere with or be vulnerable to these metal–ammonia conditions.

Careful inspection of the products listed in Table I reveals that almost all of these structural features or functional groups were compatible with the conditions of the procedure. The only carbonyl compound that resisted reduction, after phenylation, was menthone (3), which is probably due to steric interactions.[5,12] An example of overcohol,[13] a 1,3-diene system still remains which is vulnerable and reduces, as one would predict,[7] by 1,2-addition to the less substituted double bond. The phenylation–reduction of two α,β-unsaturated ketones, piperitone (7) and 4-cyclohexyl-*trans*-3-buten-2-one (8), led to mixtures of the corresponding olefin and aromatic hydrocarbon, a result hexyl-*trans*-3-buten-2-one (8), led to mixtures of the corresponding olefin and aromatic hydrocarbon, a result which did not change substantially by varying the amount of lithium used for the reduction step. The only carbonyl compound found to be completely incompatible with the reductive conditions was methyl 2-thienyl ketone. Phenylation–reduction of this ketone, which is not included in Table I,

Table I
Phenylation-Reduction of Aldehydes and Ketones

Carbonyl compd	Phenylation–reduction product	% Yield: Analytical[a]	% Yield: Isolated[b]	Comments	Carbonyl compd	Phenylation–reduction product	% Yield: Analytical[a]	% Yield: Isolated[b]	Comments
 1	 21	98	96		 11	 31	100	91	
 2	 22	95	88		 12	 32	100	91	
 3	 23	100	99	*c*, *d*	 13	 33	99	83	
 4	 24	100	94		 14	 34	100	99	
 5	 25	100	90		 15	 35	100	99	
 6	 26	98	85		 16	 36	99	90	*h*
 7	 27a.b	83	78	*c*, *e*	 17	 37	99	93	
 8	 28a.b	99	94	*f*	 18	 38	99	99	
 9	 29	100	98	*g*	 19	 39	100	96	
 10	 30	93	93		 20	 40	100	93	*c*

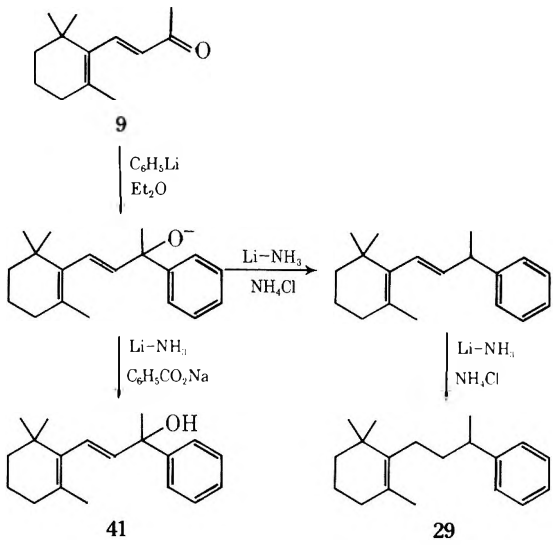
[a] Analyzed by glpc (% of volatiles). [b] Isolated by column chromatography. [c] The phenylation step was performed at *ca.* −78°. [d] This result was not altered by using an enormous excess of lithium (560 mg, 80 mg-atoms). [e] Using the normal amount of lithium (280 mg, 40 mg-atoms) or a large excess (560 mg, 80 mg-atoms) yielded an aromatic hydrocarbon fraction (83%) and 3-phenyl-1-*p*-menthen-3-ol (17%). The aromatic hydrocarbon fraction was an inseparable mixture (60:40) of 3-phenyl-1-*p*-methene (**27a**) and 3-phenyl-*p*-menthane (**27b**). Less lithium (140 mg, 20 mg-atoms) yielded the same aromatic hydrocarbon mixture (30%) and 3-phenyl-1-*p*-menthen-3-ol (70%). [f] The use of various amounts of lithium (140 mg, 20 mg-atoms; 280 mg, 40 mg-atoms; 420 mg, 60 mg-atoms; or 560 mg, 80 mg-atoms) yielded the same product 28 which was an inseparable mixture (65:35) of 1-cyclohexyl-3-phenyl-*trans*-1-butene (**28a**) and 1-cyclohexyl-3-phenylbutane (**28b**). [g] Using the normal amount of lithium (280 mg, 40 mg-atoms) yielded a mixture (30:70) of 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-phenyl-*trans*-1-butene and **29**. Less lithium (140 mg, 20 mg-atoms) resulted in the above mixture (60%) as well as the alcohol **41** (40%). Excess lithium (420 mg, 60 mg-atoms) led to **29** exclusively. [h] The aldehyde was a commercial sample of citral.

led to a complex mixture which was difficult to purify and characterize, but the data on the crude product material did indicate that the thiophene ring was being destroyed.[11b-e]

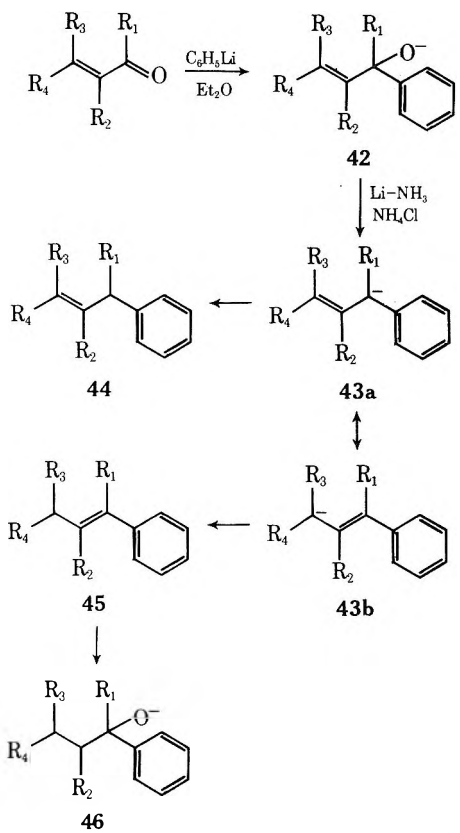
The yields, analytical (glpc) and isolated (column chromatography), listed in Table I are impressive. Generally, the only side product of the sequence is the benzyl alcohol which seems to result when the intermediate benzyl alkoxide is splattered on the walls of the reaction vessel and is not in solution during the quench. The contaminant benzyl alcohol, when present, is efficiently removed by column chromatography. In a few examples minor products were detected which stemmed from the phenylation step; these side reactions were effectively minimized by performing this operation at low temperature[14] (*ca.* −78°) and are noted in Table I.

Perhaps the most interesting mechanistic implications of this study are those involving the phenylation–reduction of the α,β-unsaturated carbonyl compounds. With these systems the reduction of the intermediate benzyl alkoxide **42** (see Scheme II) must proceed through the anion **43** which in almost every example protonates exclusively at the ben-

Scheme I



Scheme II



zylic position, trapping anion **43a**, yielding the olefin **44**. The net result is the selective introduction of a double bond β to an aromatic ring, a difficult task using classical methods. Only in two examples, **7** and **8**, does some protonation of anion **43b** occur yielding the styrene **45** which would be rapidly reduced[15] to the aromatic hydrocarbon **46**.

As a result of this study it appears that phenylation–reduction is a uniquely viable procedure for the efficient and selective synthesis of rather complex aromatic hydrocarbons. By the proper selection of the requisite carbonyl system, challenging organic structures can be rapidly assembled.

Experimental Section[16]

General Comments. The entire reaction sequence was performed under a static prepurified nitrogen atmosphere which is connected by a T tube to the assembly and to a soda-lime drying trap (then on to an oil bubbler). All glassware was oven-dried, cooled to room temperature in a large box desiccator, and then quickly assembled. Phenyllithium was generated *in situ* in the metal–ammonia reaction vessel[3] from bromobenzene and lithium in ether. Anhydrous ether was used directly from freshly opened containers. Lithium wire (0.125 in., 0.01% Na, Ventron Corp.) was hammered to a foil, cut into small pieces, and rinsed in petroleum ether just prior to use. Anhydrous ammonia was distilled into the reaction vessel. Gas chromatographic analyses (glpc) were performed on a Hewlett-Packard Model 7610A high-efficiency chromatograph (flame detector) using a 4 ft × 6 mm (all glass) 4% silicone gum rubber JCC-W-982 (methylvinyl) on 80–100 HP Chromosorb W (AW, DMCS) column. Purification of the product by column chromatography was accomplished on Woelm neutral aluminum oxide (activity grade I or II) by elution with petroleum ether. Further purification, sometimes necessary for satisfactory elemental analyses, was accomplished using a Büchi kugelrohr bulb-to-bulb distillation apparatus at reduced pressure. All boiling points are uncorrected. The assigned structure of each product is consistent with the spectral data and composition analysis. The phenylation–reduction of 3-heptanone (**1**) is described, in detail, to illustrate the general procedure.

Phenylation–Reduction of 3-Heptanone (1). 3-Phenylheptane (21). Into a metal–ammonia reaction vessel[3] containing a stirred mixture of 280 mg of lithium (40 mg-atoms, *ca.* 25 pieces which had been hammered to a foil) in 10 ml of anhydrous ether was slowly added a solution of 790 mg (5.0 mmol) of bromobenzene in 7 ml of ether. After 1 hr a solution of 285 mg (2.5 mmol) of 3-heptanone (**1**) in 8 ml of ether was slowly added and the mixture was stirred for an additional 1 hr. Ammonia (*ca.* 25 ml) was carefully, to prevent excessive splattering, distilled into the mixture and, once the dark blue color of the mixture was established,[17] *ca.* 3 g of ammonium chloride was cautiously added[18] (*ca.* 5 min) to discharge the blue color and the ammonia was allowed to evaporate. After the residue had been partitioned between aqueous NaCl and ether, the organic phase was dried ($MgSO_4$), filtered, concentrated at water aspirator pressure at 40–50°, and then analyzed (glpc). Following column chromatography 422 mg (96%) of 3-phenylheptane (**21**) was obtained as a colorless oil: bp 69–71° (1.2 mm); ir (film) 3030, 2960, 2930, 1450, and 690 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.37–6.84 (5 H, m), 2.61–2.09 (1 H, m), 1.88–1.35 (4 H, m), 1.35–0.99 (4 H, m), and two overlapping perturbed triplets centered at 0.82 (3 H, t, J = 7 Hz) and 0.73 (3 H, t, J = 7 Hz); mass spectrum *m/e* (relative intensity) 176 (M^+, 13), 147 (20), 119 (30), 105 (8), 91 (100), and 77 (5).

Anal. Calcd for $C_{13}H_{20}$: C, 88.57; H, 11.43. Found: C, 88.31; H, 11.37.

2-Phenyloctane (22). Treatment of 2-octanone (**2**) as described above yielded **22** (88%) as a colorless oil: ir (film) 3030, 2960, 2930, 1450, and 695 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.18 (5 H, apparent s), 2.66 (1 H, apparent sextet, J = 7 Hz), 1.83–1.38 (2 H, m), a doublet centered at 1.22 (3 H, d, J = 7 Hz) superimposed on an apparent broad singlet with fine splitting centered at 1.24 (8 H, broad s), and a perturbed triplet centered at 0.87 (3 H, t); mass spectrum *m/e* (relative intensity) 190 (M^+, 9), 175 (10), 105 (100), 91 (13), 77 (6), and 43 (6).

Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.29; H, 11.49.

3-Phenyl-*p*-menth-3-ol (23). Treatment of menthone (**3**) as described above, except that the phenylation step was run at *ca.* −78°, yielded **23** (99%) as a colorless oil: bp 97–98° (1.2 mm); ir (CCl_4) 3625, 3500, 3035, 2925, 1600, 1490, 1445, and 690 cm^{-1}; nmr (60 MHz, $CDCl_3$) δ 7.58–7.11 (5 H, m), 2.22–1.82 (1 H, m), 1.82–1.46 (7 H, m) on which is superimposed two broad singlets (which disappear when D_2O is added) centered at 1.60 (0.66 H, –OH) and 1.46 (0.34 H, –OH) which represent two geometric isomers, an apparent triplet centered at 1.28 (1 H, t, J = 7 Hz), and a complex set of lines from 0.97 to 0.62 (9 H, m) which appears to be three major overlapping doublets (J = 7 Hz) and three minor overlapping doublets (J = 7 Hz) representing two geometric isomers present in a ratio of about 2:1; mass spectrum *m/e* (relative intensity) 232 (M^+, 26), 217 (2), 214 (2), 147 (100), 120 (12), 105 (18), 91 (6), 77 (9), and 41 (9).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.77; H, 10.37.

5-Phenyl-1-hexene (24). Treatment of 5-hexen-2-one (**4**) as described above yielded **24** (94%) as a colorless oil: ir (film) 3070, 3030, 2960, 2930, 1642, 1603, 1492, 1450, 985, 900, 750, and 690 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.20 (5 H, apparent s), 6.18–5.48 (1 H, m), 5.18–4.97 (1 H, m), 4.92–4.75 (1 H, m), 2.72 (1 H, apparent sextet, J = 7 Hz), 2.20–1.52 (4 H, m), and 1.23 (3 H, d, J = 7 Hz); mass spectrum m/e (relative intensity) 160 (M^+, 7), 145 (5), 118 (58), 105 (100), 91 (31), and 77 (13).

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.79; H, 10.34.

2-Methyl-6-phenyl-2-heptene (25). Treatment of 6-methyl-5-hepten-2-one (**5**) as described above yielded **25** (90%) as a colorless oil: ir (film) 3030, 2960, 2930, 1600, 1495, 1450, 750, and 690 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.21 (5 H, apparent s), 5.30–4.92 (1 H, m), 2.69 (1 H, apparent q, J = 7 Hz), a broad singlet at 1.68 (3 H, s) superimposed on a broad multiplet at 2.15–1.58 (4 H, m), 1.51 (3 H, broad s), and 1.23 (3 H, d, J = 7 Hz); mass spectrum m/e (relative intensity) 188 (M^+, 65), 118 (100), 105 (93), 91 (47), 77 (14), 69 (17), 55 (23), and 41 (26).

Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 88.98; H, 10.66.

3-Phenyl-4(8)-*p*-menthene (26). Treatment of (+)-pulegone (**6**) as described above yielded **26** (85%) as a colorless oil: ir (film) 3070, 3035, 2925, 1603, 1490, 1450, and 690 cm^{-1}; nmr (100 MHz, $CDCl_3$) δ 7.37–6.98 (5 H, m), 4.13-4.00 (0.3 H, m Ph–C*H*–, equatorial proton), 3.84–3.60 (0.7 H, m, Ph–C*H*–, axial proton), *ca.* 2.60–2.10 (2 H, complex m), *ca.* 2.10–1.10 (5 H, complex m) on which are superimposed three sharp singlets at 1.73, 1.72, and 1.71 (3 H, CH_3C=, configurational and conformational isomers), and three sharp singlets at 1.45, 1.44, and 1.42 (3 H, CH_3C=, configurational and conformational isomers), and 0.86 (3 H, d, J = 5.5 Hz); mass spectrum m/e (relative intensity) 214 (M^+, 100), 199 (42), 171 (35), 157 (16), 143 (47), 129 (29), 115 (14), 91 (30), and 77 (8).

Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.39; H, 10.20.

Mixture 27. 3-Phenyl-1-*p*-menthene (27a) and 3-Phenyl-*p*-menthane (27b). Treatment of piperitone (**7**) as described above, except that the phenylation step was run at *ca.* −78°, yielded **27** (78%) as a colorless oil: bp 120–121° (1.2 mm). Careful analysis of the 100-MHz nmr spectrum of this oil indicated that it was a 60:40 mixture of 3-phenyl-1-*p*-menthene (**27a**) and 3-phenyl-*p*-menthane (**27b**). The mass spectrum confirmed this conclusion. The mixture, which indicated one peak by glpc analysis, could not be separated by column chromatography or distillation. The third product of this reaction was 3-phenyl-1-*p*-menthen-3-ol (17%). The above results were not altered by using an enormous excess of lithium (560 mg, 80 mg-atoms). Less lithium (140 mg, 20 mg-atoms) yielded the mixture **27** (30%) and the above alcohol (70%).

Mixture 28. 1-Cyclohexyl-3-phenyl-*trans*-1-butene (28a) and 1-Cyclohexyl-3-phenylbutane (28b). Treatment of 4-cyclohexyl-*trans*-3-buten-2-one (**8**) as described above yielded **28** (94%) as a colorless oil: bp 95–97° (1.1 mm). Careful analysis of the 60-MHz nmr spectrum of this oil indicated that it was a 65:35 mixture of 1-cyclohexyl-3-phenyl-*trans*-1-butene (**28a**) and 1-cyclohexyl-3-phenylbutane (**28b**), which was confirmed by the mass spectrum. The mixture, which indicated one peak by glpc analysis, could not be separated by column chromatography or distillation. Various quantities of lithium (140 mg, 20 mg-atoms; 420 mg, 60 mg-atoms; or 560 mg, 80 mg-atoms) did not alter the above result.

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-phenylbutane (29). Treatment of β-ionone (**9**) as described above, except that excess lithium (420 mg, 60 mg-atoms) was used to avoid a mixture of **29** and 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-phenyl-*trans*-1-butene, yielded **29** (98%) as a colorless oil: bp 95–98° (1.2 mm), ir (film) 3070, 3035, 2930, 1605, 1495, 1450, 755, and 690 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.21 (5 H, apparent s), 2.98–2.34 (1 H, apparent sextet, J = 7 Hz), and two broad multiplets from *ca.* 2.10 to 1.60 (6 H, m) and from *ca.* 1.60 to 1.20 (4 H, m) on which are superimposed a singlet at 1.48 (3 H, s) and a doublet at 1.27 (3 H, d), and 0.91 (6 H, s); mass spectrum m/e (relative intensity) 256 (M^+, 12), 241 (5), 123 (100), 118 (92), 105 (34), 95 (27), 91 (23), 81 (32), and 41 (25).

Anal. Calcd for $C_{19}H_{28}$: C, 88.99; H, 11.01. Found: C, 88.96; H, 11.07.

2,6-Dimethyl-4-phenyl-2,5-heptadiene (30). Treatment of phorone (**10**) as described above yielded **30** (93%) as a colorless oil: bp 80–84° (1.2 mm), ir (film) 3070, 3030, 2975, 2925, 2730, 1600, 1488, 1445, 870, 730, and 690 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.09 (5 H, apparent s), 5.21 (2 H, d, J = 9 Hz, with fine splitting of *ca.* 1.2 Hz), 4.30 (1 H, t, J = 9 Hz), and four overlapping singlets at 1.73 (3 H, s), 1.72 (3 H, perturbed s), 1.70 (3 H, s), and 1.69 (3 H, perturbed s); mass spectrum m/e (relative intensity) 200 (M^+, 100), 185 (68), 157 (65), 145 (48), 143 (68), 129 (34), and 91 (37).

Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.95; H, 10.01.

1-Cyclopropyl-1-phenylethane (31). Treatment of cyclopropyl methyl ketone (**11**) as described above yielded **31** (91%) as a colorless oil: bp 119–121° (760 mm); ir (film) 3080, 3035, 3010, 2970, 2930, 2880, 1605, 1490, 1450, 1015, 810, 750, and 690 cm^{-1}; nmr (220 MHz, CCl_4, with and without TMS) δ 7.25–7.00 (5 H, m), 1.95 (1 H, quintet, J = 7 Hz), 1.32 (3 H, d, J = 7 Hz), 1.02–0.73 (1 H, m), 0.61–0.30 (2 H, m), and 0.25–0.02 (2 H, m); mass spectrum m/e (relative intensity) 146 (M^+, 27), 131 (31), 118 (98), 117 (76), 105 (100), 91 (70), 77 (42), 51 (34), and 39 (42).

Anal. Calcd for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.26; H, 9.71.

1-Phenylundecane (32). Treatment of 1-undecanal (**12**) as described above yielded **32** (91%) as a colorless oil: bp 92–94° (1.1 mm); ir (film) 3035, 2970, 2930, 2860, 1455, and 690 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.08 (5 H, apparent s), 2.55 (2 H, perturbed t, J = 7 Hz), 1.9–1.4 (2 H, m), 1.27 (16 H, broad s), and 0.89 (3 H, perturbed t); mass spectrum m/e (relative intensity) 232 (M^+, 8), 92 (50), 91 (100), 69 (62), 55 (34), 43 (42), and 41 (53).

Anal. Calcd for $C_{17}H_{28}$: C, 87.86; H, 12.14. Found: C, 87.86; H, 12.07.

1-Phenyl-2-methylpentane (33). Treatment of 2-methyl-1-pentanal (**13**) as described above yielded **33** (83%) as a colorless oil: bp 60–62° (1.2 mm); ir (film) 3035, 2960, 2930, 2880, 1604, 1495, 1450, 720, and 690 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.09 (5 H, apparent s), 2.64 (1 H, d of d, J = 13 and 6 Hz), 2.27 (1 H, d of d, J = 13 and 7 Hz), a broad multiplet from *ca.* 2.0 to 1.4 (1 H, m), 1.4–1.05 (4 H, m), and a doublet at 0.82 (3 H, d, J = 6.5 Hz) superimposed on a perturbed triplet at 0.88 (3 H, t); mass spectrum m/e (relative intensity) 162 (M^+, 24), 119 (2), 92 (100), 91 (48), and 43 (44).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.78; H, 11.08.

11-Phenyl-1-undecene (34). Treatment of 10-undecen-1-al (**14**) as described above yielded **34** (99%) as a colorless oil: ir (film) 3075, 3040, 2920, 2865, 1640, 1605, 1495, 1450, 900, and 690 cm^{-1}; nmr (220 MHz, CCl_4) δ 7.23–6.91 (5 H, m), 5.82–5.59 (1 H, m), 5.00–4.77 (2 H, m), 2.55 (2 H, t, J = 7 Hz), 2.00 (2 H, apparent q, J = 7 Hz), 1.68–1.48 (2 H, m), and 1.45–1.14 (12 H, broad s); mass spectrum m/e (relative intensity) 230 (M^+, 11), 131 (16), 117 (16), 104 (63), 105 (18), 92 (48), 91 (100), 69 (37), 55 (19), and 41 (27).

Anal. Calcd for $C_{17}H_{26}$: C, 88.63; H, 11.37. Found: C, 88.36; H, 11.63.

α-(2,6,6-Trimethyl-1-cyclohexen-1-yl)toluene (35). Treatment of β-cyclocitral (**15**) as described above yielded **35** (99%) as a colorless oil: ir (film) 3070, 3035, 2965, 2935, 2870, 1605, 1495, 1450, and 690 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.17 (5 H, broad s), 3.49 (2 H, broad s), 2.30–1.92 (2 H, broad m), a complex multiplet at 1.91–1.60 (2 H, m), 1.53 (3 H, broad s), 1.28 (3 H, t, J = 7 Hz), and 0.92 (6 H, s); mass spectrum m/e (relative intensity) 214 (M^+, 75), 199 (100), 143 (14), 123 (43), 105 (15), and 91 (46).

Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.35; H, 10.34.

1-Phenyl-3,7-dimethyl-2,6-octadiene (36). Treatment of citral (**16**), which is a mixture of neral and geranial, as described above yielded **36** (90%) as a colorless oil: ir (film) 3070, 3035, 2970, 2925, 1445, 715, and 685 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.19 (5 H, broad s), 5.57–4.97 (2 H, complex m), 3.33 (2 H, broad d, J = 7.4 Hz), 2.23–1.98 (4 H, m), 1.69 (6 H, broad s), and 1.60 (3 H, broad s); mass spectrum m/e (relative intensity) 214 (M^+, 91), 199 (4), 145 (98), 129 (49), 123 (83), 91 (69), 69 (100), and 41 (49).

Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.30; H, 10.27.

4-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-methyl-1-phenyl-*trans*-2-butene (37). Treatment of C_{14}-aldehyde (**17**) as described above yielded **37** (93%) as a colorless oil: bp 95–97° (1.1 mm); ir (film) 3035, 2965, 2920, 2860, 1601, 1492, 1450, 720, and 690 cm^{-1}; nmr (220 MHz, CCl_4) δ 7.25–6.93 (5 H, m), 5.09 (1 H, t, J = 12 Hz), 3.21 (2 H, s), 2.69 (2 H, d, J = 12 Hz), 2.00–1.86 (2 H, m), 1.68–1.36 (4 H, m) on which are superimposed two singlets at 1.53 (3 H, s) and 1.51 (3 H, s), and 0.95 (6 H, s); mass spectrum m/e (relative intensity) 268 (M^+, 100), 253 (17), 225 (8), 198 (4), 177 (92), 123 (46), 121 (38), 107 (35), and 91 (60).

Anal. Calcd for $C_{20}H_{28}$: C, 89.49; H, 10.51. Found: C, 89.31; H, 10.49.

1-(4-*tert*-Butylphenyl)-3-phenyl-2-methylpropane (38).

Treatment of 3-(4-*tert*-butylphenyl)-2-methyl-1-propanol (**18**) as described above yielded **38** (99%) as a colorless oil: ir (film) 3090, 3070, 3035, 2975, 2925, 2860, 1601, 1490, 1450, 1260, 722, and 689 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.18 (5 H, broad s) superimposed on an AB pattern with the first doublet centered at 7.31 (2 H, d, J = 8.5 Hz) and the second at 7.06 (2 H, d, J = 8.5 Hz), 2.92–2.54 (1 H, m), 2.44 (2 H, d, J = 7.5 Hz), 2.26–1.78 (2 H, m), 1.29 (9 H, s), and 0.82 (3 H, d, J = 6.2 Hz); mass spectrum *m/e* (relative intensity) 266 (M^+, 58), 251 (67), 175 (34), 162 (13), 147 (48), 132 (13), 119 (28), 105 (12), 92 (47), 91 (100), 57 (5), and 41 (25).

Anal. Calcd for $C_{20}H_{26}$: C, 90.17; H, 9.84. Found: C, 89.89; H, 9.75.

***p*-Methoxydiphenylmethane (39).** Treatment of *p*-anisaldehyde (**19**) as described above yielded **39** (96%) as a colorless oil: ir (film) 1610, 1586, 1510, 1495, 1240, 1172, 1030, 830, 790, 760, 718, and 690 cm^{-1}; nmr (60 MHz, CCl_4) δ 7.19 (5 H, s), an AB pattern with the first doublet centered at 7.07 (2 H, d, J = 9 Hz) and the second at 6.76 (2 H, d, J = 9 Hz), 3.86 (2 H, s), and 3.65 (3 H, s); mass spectrum *m/e* (relative intensity) 198 (M^+, 100), 197 (40), 183 (12), 167 (30), 121 (28), and 91 (12).

Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.83; H, 7.10.

2-Benzylfuran (40). Treatment of furfural (**20**) as described above, except that the phenylation step was run at *ca.* −78°, yielded **40** (93%) as a colorless oil: ir (film) 1595, 1505, 1492, 1450, 1065, 1001, 710, and 690 cm^{-1}; nmr (60 MHz, CCl_4) a multiplet at δ 7.22–6.97 (1 H, m) on which is superimposed a singlet at 7.14 (5 H, s), 6.22–6.05 (1 H, m), 5.92–5.77 (1 H, m), and 3.86 (2 H, s); mass spectrum *m/e* (relative intensity) 158 (M^+, 100), 129 (65), 115 (23), 103 (4), 91 (9), and 81 (19).

Anal. Calcd for $C_{11}H_{10}O$: C, 83.52; H, 6.37. Found: C, 83.76; H, 6.51.

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Registry No.—**1,** 106-35-4; **2,** 111-13-7; **3,** 89-80-5; **4,** 109-49-9; **5,** 110-93-0; **6,** 89-82-7; **7,** 89-81-6; **8,** 41437-84-7; **9,** 14901-07-6; **10,** 504-20-1; **11,** 765-43-5; **12,** 112-44-7; **13,** 123-15-9; **14,** 112-45-8; **15,** 432-25-7; **17,** 14398-40-4; **18,** 80-54-6; **19,** 123-11-5; **20,** 98-01-1; **21,** 2132-85-6; **22,** 777-22-0; **23,** 18368-90-6; **24,** 30134-52-2; **25,** 53210-18-7; **26,** 53210-19-8; **27a,** 53210-20-1; **27b,** 53210-21-2; **28a,** 53210-16-5; **28b,** 53210-22-3; **29,** 53210-23-4; **30,** 53210-24-5; **31,** 16510-30-8; **32,** 6742-54-7; **33,** 39916-61-5; **34,** 53210-25-6; **35,** 53210-26-7; **36,** 53210-27-8; **37,** 53210-15-4; **38,** 53210-28-9; **39,** 834-14-0; **40,** 37542-92-0; bromobenzene, 108-86-1; neral, 106-26-3; geranial, 141-27-5.

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(1) (a) Part I: S. S. Hall and S. D. Lipsky, *J. Chem. Soc., Chem. Commun.*, **1242** (1971). (b) Part II: S. S. Hall and S. D. Lipsky, *J. Org. Chem.*, **38, 1735** (1973). (c) S. S. Hall and S. D. Lipsky, *Org. Syn.*, in press.

(2) Part III: S. S. Hall, *J. Org. Chem.*, **38,** 1738 (1973).

(3) For a useful general discussion of metal–ammonia experimental techniques see M. Smith in "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N.Y. 1968, pp 98–105.

(4) For a discussion of the mechanism of the reduction see (a) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971); (b) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36,** 2588 (1971).

(5) In previous unpublished work (S. S. Hall and G. H. Small) certain sterically hindered benzyl alcohols were found resilient to these reducing conditions.

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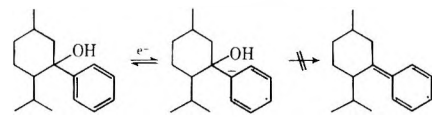
(12) During the reduction of the benzyl alcohol intermediate, the benzyl carbon must assume an sp^2 configuration.



(13) That no reduction occurs until the ammonium chloride quench was established by repeating the experiment using sodium benzoate as the quenching agent; which resulted in the isolation of the corresponding phenylated compound 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-phenyl-*trans*-1-buten-3-ol (**41**) as the sole product: nmr (60 MHz, CCl_4) δ 7.64–7.10 (5 H, m), 6.14 (1 H, d with fine splitting, J = 16 Hz), 5.69 (1 H, d, J = 16 Hz), 2.77 (1 H, broad peak which disappears when D_2O is added), broad multiplets at 2.15–1.79 (2 H) and 1.79–1.31 (4 H) on which is superimposed a broad singlet at 1.60 (6 H, s, 2 CH_3–), and 0.97 (6 H, s, 2 CH_3–). See also footnote *g* of Table I.

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(15) See (a) ref 2; (b) ref 3, pp 118–119; (c) H. Smith, "Organic Reactions in Liquid Ammonia. Chemistry in Nonaqueous Ionizing Solvents," Vol. I, Part 2, Wiley, New York, N.Y., 1963, p 228.

(16) The ir spectra were determined with a Beckman Model IR-10 infrared recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Associates Model A-60 nmr spectrometer, at 100 MHz with a Varian Associates Model XL-100 nmr spectrometer and at 220 MHz with a Varian Associates HR-220 nmr spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with a Consolidated Electronics Corp. Model 110-21B mass spectrometer and a Varian Associates Model CA5 mass spectrometer with a Varian Associates Model 620/i computer attachment.

(17) Normally *ca.* 10 min elapsed before proceeding with the quenching step, although the time interval does not seem too critical.

(18) The ammonium chloride was most conveniently introduced by attaching a glass tube filled with the salt to a side arm with Tygon tubing. When the ammonium chloride is to be added, the tube is raised and tapped gently to smoothly introduce the quenching agent. Should this step start to become violent, the addition and the vigorous stirring should be momentarily stopped to avoid an eruption.

4-Homoisotwistane, 6,7-exo-Trimethylenebicyclo[3.2.1]octane, and Homoadamantane as Intermediates in Brønsted Acid Catalyzed Adamantane Rearrangement of Tricycloundecanes

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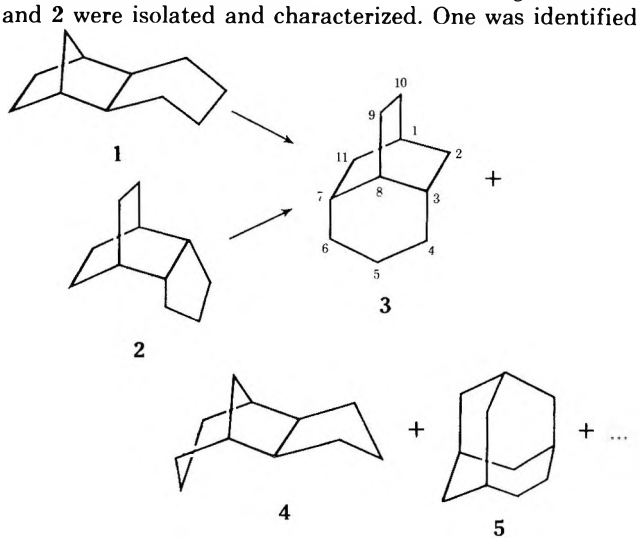
4-Homoisotwistane (tricyclo[5.3.1.0^{3,8}]undecane) (**3**), 6,7-*exo*-trimethylenebicyclo[3.2.1]octane (**4**), and homoadamantane (**5**), together with several, as yet unidentified tricycloundecanes, were discovered to be intermediates in the adamantane rearrangement of 2,3-*exo*-tetramethylenenorbornane (**1**) and 2,3-trimethylenebicyclo[2.2.2]octane (**2**). ^{13}C nmr spectroscopy was the main tool in the structure determination of **3** and **4**. The structure of **4** was further confirmed by comparison with an independently synthesized authentic specimen. Brønsted acids (trifluoromethanesulfonic acid and sulfuric acid) were found to catalyze the rearrangement of these tricycloundecane precursors with almost quantitative yields of the products, the catalysis being milder and more specific than that by aluminum halides. A high yield synthesis of **3** was accomplished by a selective rearrangement of **2** catalyzed by sulfuric acid. An outline of the reaction scheme was deduced from the product studies of these Brønsted acid catalyzed rearrangements.

Acid-catalyzed isomerization of polycyclic saturated hydrocarbons to adamantanes (so-called adamantane rearrangement) has been widely studied since the discovery of the reaction by Schleyer.[1] Elucidation of the mechanism of the reaction, however, seems to have been less fruitful, except for the results by Whitlock[2] and Schleyer[3] on $C_{10}H_{16}$ rearrangement, when compared with many successful synthetic approaches in which a number of precursors has been found to give diamonoid molecules in good yields.[4] The difficulty involved in mechanistic studies will be fully understood by considering the abundance of isomeric polycycloalkanes[5] which may take part, to the degree their relative stabilities and reactivities will allow, in the rearrangement consisting of a complex network of competitive and/or consecutive reaction pathways. We also have been interested in the problem and studied mainly the rearrangement of C_{11} tricyclic hydrocarbons.

Only two tricycloundecane precursors, 2,3-*exo*-tetramethylenenorbornane (**1**)[6-9] and 2,3-*endo*-tetramethylenenorbornane,[9] were hitherto known to undergo adamantane rearrangement.[10] However no intermediate had been identified[12] until the existence of 4-homoisotwistane (**3**)[14] was established by Schleyer[13] in the rearrangement of **1**, and independently by us[15] in the rearrangement of **1** and 2,3-trimethylenebicyclo[2.2.2]octane (**2**), under aluminum chloride catalysis.

Now two further intermediates in the rearrangement of **1** and **2** were isolated and characterized. One was identified as homodamantane (**5**), which had been looked for but in vain in tricycloundecane rearrangements.[12,13] The other was determined by ^{13}C nmr spectroscopy to be one of four possible tricycloundecane isomers including 5,6-*exo*-trimethylenebicyclo[3.2.1]octane (**4**). Three other possibilities than **4** was unambiguously excluded by an independent synthesis of an authentic **4**.



Brønsted acids (trifluoromethanesulfonic acid and sulfuric acid) were found to be effective catalysts for the rearrangement of C_{11} tricyclic hydrocarbons. Indeed the sulfuric acid catalyzed isomerization of tetrahydro-Binor-S to diamantane[16] was the only example of Brønsted acid catalysis of the adamantane rearrangement of hydrocarbons. Although trifluoromethanesulfonic acid gave almost similar intermediate distributions as, but more slowly catalyzed the rearrangement than, aluminum chloride, sulfuric acid catalysis was fairly specific with respect to both reactant and product. Thus **2** was isomerized to **3** in a high yield in the presence of sulfuric acid.[17]

Slow catalysis by Brønsted acid made easier the study of time–conversion relationships in the rearrangement. Further isomerizations of isolated intermediates revealed the presence of some quasi-equilibriums. These results led us to draw an outline of the rearrangement scheme.

4-Homoisotwistane (3). Isomerization of **1** with 20 mol % of aluminum chloride in methylene chloride for 20 min at ambient temperature gave, together with a small amount of methyladamantanes, 45% **3** and three other major components in the amount of 23, 18, and 6%, respectively (run 1, Table I). The ir, ^{1}H nmr, and mass spectra did not tell much about the structure of **3**, except that molecular ion peak with relative intensity of 100 in the mass spectrum suggested a reasonably symmetrical cage structure. The ^{13}C nmr spectra of **3** showed the presence of eight different kinds of carbon atoms and the absence of methyl group in the molecule. Of the possible 70 tricycloundecanes containing neither three- nor four-membered rings,[5] only two isomers, **3** and **6**, are consistent with the above ^{13}C nmr spectra.

The structure **3** seems to explain better the methylene carbon resonance in an abnormally high field (15.2 ppm) than the alternative, **6**, does. Thus the methylene carbon resonance was assigned to 5-carbon atom in **3**, based on the calculated value (15.8 ppm) for the atom. The effect of 3(a)- and 4(e)-methyl group (or corresponding methylene groups in the fused ring system) on the chemical shift

Table I
Distribution of Intermediates in the Rearrangement of Tricycloundecanes[a]

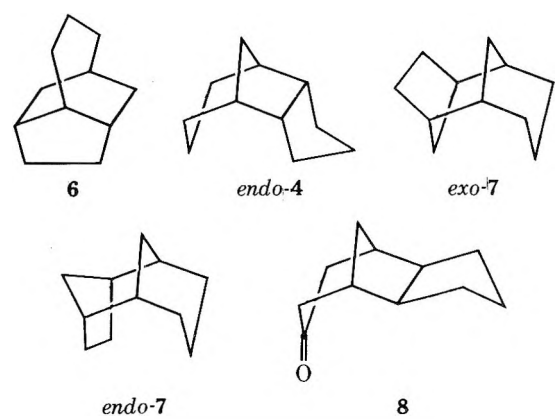
Run	Reactant	Reaction time, hr	Product,[b] %[c] Unknown A	1-Methyl-adamantane	Unknown B	Unknown C	2-Methyl-adamantane	4	1	3[d]	Unknown D[d]	2[d]	Unknown E	5
						Aluminum Chloride								
1	1[e]	0.3	0.6	2.4	23.0	17.6	0.6	6.1		44.7	3.8			1.2
		1.0		96.0			4.0							
2	2[e]	0.2			29.2	14.6		5.1		44.4	3.5			1.2
		1.0		96.3			3.7							
						Trifluoromethanesulfonic Acid								
3	1[f]	0.1			4.3	2.8			74.5	18.4				
		1.0	1.5	0.3	23.8	17.1	1.7	1.7	0.6	45.0	5.3			1.5
		24	2.6	6.8	18.9	15.6	6.0	6.8		37.2	2.8			2.1
4	2[g]	1.0			2.8	5.0		1.5		29.2	21.5	17.5	20.2	
		24	2.2	1.6	19.3	16.6	2.4	5.4		46.9	3.2			2.2
5	2[f]	1.0	0.3	1.0	8.1	16.6	1.4	3.9		60.2	4.4			2.3
		24	2.3	6.3	18.5	16.2	5.9	5.9		36.6	3.0			2.1
6	3[f]	1.0	0.5	1.6	10.3	19.6	3.2	4.1		51.8	4.5			2.3
		6.0	1.0	4.4	15.7	18.9	4.6	6.2		41.1	3.6			2.6
		24	2.4	5.3	19.6	16.8	5.8	6.5		36.3	2.8			1.8
		100	10.0	20.3	12.5	8.0	25.2	5.5		15.0	1.3			1.2
7	4[f]	5.0	1.7	2.1	7.3	7.5	2.5	53.4		24.2				0.7
		38	1.8	10.0	13.7	11.9	11.6	18.8		26.6	2.0			1.5
						Sulfuric Acid								
8[h]	2	2								38.3	20.7	28.7	8.9	
		7				3.5				93.5	2.8			

[a] 200 mg of reactant in 10 ml of methylene chloride at reflux, unless otherwise noted. [b] Yields of the intermediate mixtures as well as the final products (methyladamantanes) were always quantitative. Products are analyzed by conventional vpc and aligned in the order of the increasing retention time. See, however, footnote *d*. [c] That of the vpc peak area. [d] **3**, unknown D, and **2** could not be separated from each other by the usual vpc, but on a Golay column, from which proportions of **3**, unknown D, and **2** were calculated. [e] With 0.2 molar equiv to reactant of $AlCl_3$. The reaction was run at ambient temperature. [f] With 4.0 molar equiv of CF_3SO_3H. [g] With 1.0 molar equiv of CF_3SO_3H. [h] 500 mg of **2**, 3.2 ml of carbon tetrachloride, and 5 g of 95% sulfuric acid were stirred at ambient temperature. The reaction was heterogeneous, carbon tetrachloride layer being analyzed. The product was accompanied by some tarry materials, and the yield of crude **3** on isolation amounted to 81%.[17]

change of 1-carbon atom in chair form cyclohexane (26.9 ppm) has been calculated as −5.4 and −0.3 ppm, respectively.[18] A rational assumption that the additivity of chemical shifts in polycycloalkanes such as adamantane[19] also holds for **3** enabled us to calculate the chemical shift of the 5-carbon atom: 26.9 − 2 × 5.4 − 0.3. A good agreement between the observed and the calculated values indicates the existance of a trisubstituted cyclohexane partial structure and, hence, the structure **3** for the compound. The structure was later confirmed by the comparison of melting point and ^{13}C nmr spectrum with those described in the literature.[13,14]

6,7-*exo*-Trimethylenebicyclo[3.2.1]octane (4). The sixth peak (6.1 %) in run 1 (Table I) was isolated and found to be homogeneous on several vpc columns. A large scale experiment allowed the separation and purification of the component on a preparative vpc. The ^{13}C nmr spectrum of the compound showed the presence of seven different kinds of carbon atoms among which three kinds had a relative spectral intensity of one. All of these three carbon atoms exhibited triplet absorptions in the off-resonance proton decoupled spectrum. Absence of methyl group was also indicated. The isomers[5] corresponding to the spectra are limited to four compounds: **4**, its *endo*-trimethylene isomer (*endo*-**4**), and 2,4-*exo*- and -*endo*-ethanobicyclo[3.3.1]nonane (*exo*-**7** and *endo*-**7**, respectively).

Since it is quite difficult to assign to the compound any of the four structures only by spectral method owing to the paucity in data for reference compounds, unequivocal synthesis seemed to be the shortest approach to the problem. We chose to synthesize **4** at first because no authorized route was established for the ever unknown **7**'s, and because *endo*-**4** might have little chance to be trapped as an intermediate owing to the relative instability. Synthesis of **4** was started by obtaining 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-3-one (**8**) by the application of the method of Jefford, *et al.*,[20] to 5,6-*exo*-trimethylenenorborn-2-ene.[21] The ketone **8** was also obtainable, as a mixture with 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-2-one and higher homologous ketones, on the ring expansion[22] of 5,6-*exo*-trimethylenenorbornan-2-one[23] by diazomethane. Wolff–Kishner reduction[24] of **8** gave an authentic **4**. Spectral properties, refractive index, and retention times on some



vpc columns of thus synthesized 4 were in complete agreement with those of the isolated intermediate under examination.

Homoadamantane (5). The last eluted component in the reaction mixture of run 1 was identified as homoadamantane (5) by comparison with an authentic specimen (retention times on vpc, melting point, and spectral properties). 5 has escaped[12,13] from the scrutiny of researchers probably because of its scarcity in reaction mixtures.

Unknowns. Structures of the compounds from other vpc fractions were left undetermined. This is mainly because they are mixtures. Capillary (Golay) column vpc revealed the presence of multiple components in them: unknown A, three; unknown B, three at the very beginning, and two in the later stage, of the rearrangement; and unknown C, four. Each of unknown D (Table I, footnote *d*) and E gave only one peak also in Golay vpc. Mass spectra are the only information available to us on these components at present, which were measured on a combined Golay vpc–mass spectrometer. All of the twelve components gave a molecular ion peak of *m/e* 150 with correct isotopic abundance corresponding to $C_{11}H_{18}$.[25] It was also possible by Golay vpc–mass spectrometry to establish the identities of each components from different precursors, 1–4.

^1H nmr spectra were taken on each of the isolated unknown fractions (A, B, C, and E) to show that the resonance was entirely absent in olefinic proton regions for the unknowns. These spectroscopic evidences indicate that no appreciable disproportionation had occurred under present reaction conditions.

Trifluoromethanesulfonic Acid Catalyzed Rearrangement of 2,3-*exo*-Tetramethylenenorbornane (1) and 2,3-Trimethylenebicyclo[2.2.2]octane (2). One of the reasons why we were successful in the detection of intermediates in adamantane rearrangements would lie in the use of milder catalyst system than had been used so far.[4] As an extention of this reasoning, it might be possible to detect a larger number of intermediates by making use of still milder catalyst systems. Selection of the catalyst may be made among Brønsted acids, trifluoromethanesulfonic acid, the strongest ever existed, being tried at first.

Trifluoromethanesulfonic acid in refluxing methylene chloride was found to catalyze the rearrangement of 1 and 2. Contrary to our expectations, the distribution of intermediates in these reactions was almost the same as in those catalyzed by aluminum chloride. However, a few characteristic features are to be noted. The catalyst has a very low activity in giving rise to methyladamantanes. Comparison of runs 1 and 3 shows that although both reactions proceed similarly up to the disappearence of 1, further reaction of the intermediates is very sluggish under trifluoromethanesulfonic acid catalysis. The catalyst also clearly demonstrated the difference between the reactivities and the reaction pathways in 1 and 2. 1 was so unreactive in the presence of 1.0 molar equiv of the catalyst that it was impracticable to study the reaction with this amount of the catalyst. 2 gave a new component (unknown E) and an increased proportion of unknown D (run 4), while none was observed with 1.

Trifluoromethanesulfonic Acid Catalyzed Rerrangement of the Isolated Intermediates (3 and 4). Treatment of the isolated intermediates, 3 and 4, with trifluoromethanesulfonic acid revealed an interesting feature of the rearrangement. The intermediate distributions in the reaction of 3 at 1 hr and 24 hr (run 6) are almost identical with those of 1 at 1 hr and 24 hr (run 3) as well as those of 2 with 4.0 *M* catalyst at 1 hr and 24 hr (run 5), respectively. The reaction of 4 (run 7) gave a little different intermediate distribution at the beginning of the reaction, but the proportion of unknowns A, B, C, and D, 3, and 5 in run 7 at sufficiently long reaction time (38 hr) is in quite a good agreement with that of the corresponding components in the reaction of 3 at a long reaction time (run 6, 24 hr) as well as those of the same components in the long reaction of 1 and 2.

Sulfuric Acid Catalyzed Rearrangement of 2,3-Trimethylenebicyclo[2.2.2]octane (2). A Convenient Synthesis of 4-Homoisotwistane (3). Sulfuric acid was also found to catalyze the rearrangement. The catalysis, however, was fairly specific with respect to reactant and product. Under the reaction conditions studied (Table I, footnote *h*), only 2 was isomerized, while 1, 3, and 4 were quite unreactive. Substitution of carbon tetrachloride in run 8 for methylene chloride did not change the product distribution at all, but gave a little inferior yield of 3 accompanied by an increased amount of tarry materials. These results led us to establish a convenient synthesis[17] of 3 which otherwise could be obtained so far only with difficulty.[13–15] Formation of unknown E and an increased proportion of unknown D at the beginning of the reaction (run 8, 2 hr) are in common with the reaction of 2 catalyzed by a small amount of trifluoromethanesulfonic acid (run 4, 1 hr); but the absence of unknowns A and B and 4 in run 8 is to be noted.

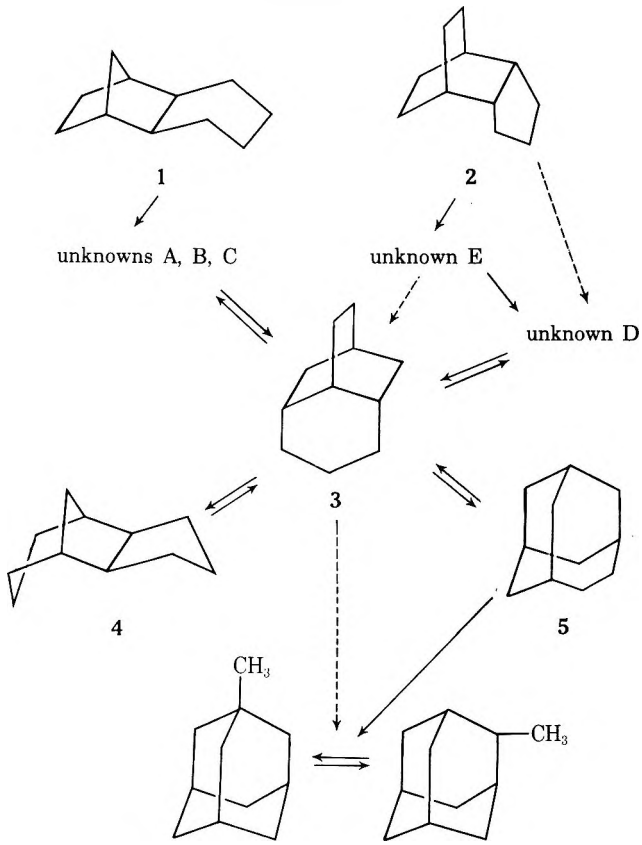
Discussion

Trifluoromethanesulfonic acid does not seem to have been examined as a catalyst in the adamantane rearrangement of tricyclic hydrocarbons. Sulfuric acid was successfully used for hydride transfer reduction–rearrangements,[14,26] but only a single example[16] can be cited for the sulfuric acid catalysis of adamantane rearrangement. Aspects of trifluoromethanesulfonic acid catalysis, especially concerning the product distributions, are fundamentally identical with those of aluminum chloride catalysis, although use of trifluoromethanesulfonic acid led to the detection of a new isomer, unknown E, in the reaction of 2 (run 4). However, this apparent difference vanishes if we expect unknown E to appear midway between 2 to 3 and to disappear quickly under the influence of stronger catalyst, aluminum chloride.

Sulfuric acid shows a little different catalytic activity from those of aluminum chloride and trifluoromethanesulfonic acid (runs 2, 4, and 8). Absence of unknown A and B as well as 4 in run 8 indicates that these three can be formed from 3 under aluminum chloride and trifluoromethanesulfonic acid catalysis, but are not under the influence of sulfuric acid. Difference between the activities of sulfuric acid and other two catalysts is better demonstrated in the formation of methyladamantanes from 3. Aluminum chloride and trifluoromethanesulfonic acid gave methyladamantane, although the reaction was very sluggish with the latter catalyst, while sulfuric acid did not. On the other hand, the fact also suggests faster reactions of 1 and 2 to 3 than that of 3 to methyladamantanes.

It is to be noted that 1 and 2 gave a similar distribution of intermediates on prolonged reaction. These proportions of intermediates are, in turn, quite similar to those in the further isomerization of either 3 or 4. An explanation for the results would be that the product distribution was the same as in the further isomerization of once formed 3, and this indicates that 3 would be one of the key intermediates in the whole sequence of the rearrangement. That 4 was formed from 3, but not directly from 1 or 2, is most probable in view of an almost exclusive formation of 3 from 2 (run 8), slow formation of 3 from 4 (run 7), and increase of

the amount of 4 after 1 or 2 had disappeared. An outline of the reaction scheme may be drawn based on these results.



The reactants 1 and 2 are quickly and irreversibly converted *via* unknowns to 3 which then slowly isomerized to final methyladamantanes. The rearrangement of 3 is indeed so slow under Brønsted acid catalysis that we may regard 3 to be in quasi-equilibriums with 4, 5, and some unknowns, the equilibriums slowly leaking to give methyladamantanes. 1 isomerizes to 3 with the intermediacy of unknowns A, B, and C, which, in turn, are in equilibrium with 3. 2 isomerizes to 3 *via* unknown E, and then *via* unknown D which is also in equilibrium with 3. It is not clear at present whether or not there exist any direct route from 2 to unknown D and that from unknown E to 3. 4 is most probably formed from and in equilibrium with 3. It is noteworthy that sulfuric acid fails to set up the equilibriums between 3 on one hand, and 4, unknown A, or unknown B on the other.

The scheme is quite obscure between 3 and methyladamantanes. What is certain at present is the intermediacy of 5. 3 gives rise to and is in equilibrium with 5, as shown by Majerski in his isomerization of homoadamant-4-yl cation to 3 and 2-methyladamantane[14] as well as in our experiments.[27] It seems to have been believed that 5 is the immediate precursor to methyladamantanes in view of the facile isomerization of 5 to methyladamantanes.[6b,13,14,28] Present experiments could not demonstrate whether or not the implicit allegation was correct, nor prove the presence of any pathways from 3 to methyladamantanes without the intermediacy of 5.

Present results are to be considered as a demonstration of the complexity, rather than the clear elucidation, of tricycloundecane rearrangements. Structures of unknowns and equilibriums as well as rate constants should be determined before the problem has been solved. However it is still evident from our incomplete studies that 3 is one of the largest energy minima on the tricycloundecane rearrangement surface.[13]

Experimental Section

All melting and boiling points are uncorrected. Infrared spectra were obtained for neat samples on a Hitachi 215 spectrophotometer. ^{1}H nmr spectra were obtained on a Varian T-60 instrument using deuteriochloroform as solvent. All chemical shifts are reported in parts per million downfield from an internal TMS standard (δ). ^{13}C nmr spectra were obtained at 15.1 MHz on a Varian NV-14 spectrometer. Mass spectra were measured on a Hitachi RMU-6D spectrometer with 75-eV ionization voltage. The vpc was accomplished on a Shimazu GC-4B-PTF chromatograph employing columns (¼ in. × 6 ft) packed with 60–80 mesh Chromosorb W containing 30% silicone SE-30, Carbowax 20M, Apiezon L, or DEGS. Golay vpc was done on a Perkin-Elmer 700 instrument using columns (0.01 in. × 150 ft) packed with Apiezon L or silicone SE-30 and operated between 60 and 70°. Golay vpc–mass spectrometry was made with a combination of JEOL JGC-20-KP gas chromatograph and JMS-D100 mass spectrometer. Preparative vpc was done on a Varian Aerograph 700 instrument. Elemental analyses were made on an automatic Yanagimoto CHN MT-2.

Materials. Trifluoromethanesulfonic acid is a commercial product of 3M Co. Methylene chloride was dried over anhydrous calcium chloride and distilled immediately before use. 2,3-Trimethylenebicyclo[2.2.2]octane (2) was prepared[17] by hydrogenation of the Diels–Alder adduct[29] of cyclopentadiene and cyclohexa-1,3-diene and purified on the preparative vpc. Homoadamantane (5) was synthesized according to the method of Stetter.[30] 4-Homoisotwistane (3) was obtained by the rearrangement of 2,3-trimethylenebicyclo[2.2.2]octane (2) catalyzed by sulfuric acid.[17] An authentic specimen of 6,7-*exo*-trimethylenebicyclo[3.2.1]octane (4) was prepared by the application of the established synthesis of bicyclo[3.2.1]octan-3-one[20] to 5,6-*exo*-trimethylenenorborn-2-ene[21] as described below.

4-Homoisotwistane (3). A mixture of 50 g (0.33 mol) of crude 2, 320 ml of carbon tetrachloride, and 500 g of 95% sulfuric acid was stirred at ambient temperature for 7 hr. The organic layer was separated, and the sulfuric acid layer was extracted once with 100 ml of carbon tetrachloride. The combined organic layer and carbon tetrachloride extract were washed successively with each 100 ml of water, saturated sodium bicarbonate solution, and water and then dried over anhydrous calcium chloride. Carbon tetrachloride was evaporated off under slightly reduced pressure, and the residue was fractionally distilled *in vacuo* through a 1-ft Vigreux column. The fraction boiling at 92–94° (16 mm) gave 40.5 g (81%) of crude 3, mp 55–58°. The purity of crude 3 thus obtained was 94%, as calculated from the area ratio in the Golay vpc. Slow sublimation [60° (19 mm)] gave an analytical sample: mp 62–63° (lit. mp 56–58,[14] 57–59,[14] 66.6–67°[13]); ir 2925, 2890, 2870, 2850, 1480, 1465, 1450, 1440, 1340, 975, 940, 895, 845, cm^{-1}; ^{1}H nmr δ 1.0–2.0 (complex m); ^{13}C nmr (multiplicity, rel intensity) 15.2 (t, 1), 24.8 (d, 1), 26.3 (t, 1) 27.1 (t, 1), 30.9 (d, 2), 31.9 (t, 2) 32.2 (t, 2), 33.1 (d, 1); mass spectrum *m/e* (rel intensity) 150 (100, M$^+$), 122 (39), 121 (39), 109 (12), 108 (16), 107 (19), 93 (27) 81 (27), 80 (46), 79 (40), 67 (35), 55 (18), 41 (40).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.8; H, 12.2.

3,4-Dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene. To a mixture of 26.8 g (0.2 mol) of 5,6-*exo*-trimethylenenorborn-2-ene,[21] 40 g (0.74 mol) of sodium methoxide, and 150 ml of petroleum ether was added with efficient stirring 126 g (0.65 mol) of ethyl trichloroacetate at 0° over a period of 3 hr. The mixture was stirred at −5 to 0° for a further 4 hr and then allowed to warm gradually to ambient temperature overnight with continuously stirring. The reaction mixture was poured onto an equal volume of ice–water and the resulting mixture was set aside to separate an organic layer, the aqueous layer being extracted four times with ether. The combined organic layer and ether extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removal of the solvent under slightly diminished pressure at room temperature, the residue was fractionally distilled to give 22.5 g (50%) of 3,4-dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene: bp 138–140° (5 mm); $n^{25.6}$D 1.5320; ir 2945, 2850, 1620 (C=C), 1320, 1050, 958, 798, 693 cm^{-1}; ^{1}H nmr δ 0.9–3.0 (m, 12), 4.15 (d, 1, J = 3 Hz, CHCl), 6.12 (d, 1, J = 7 Hz, C=CH): mass spectrum *m/e* (rel intensity) 218 (3), 216 (4), 115 (14), 114 (9), 113 (41), 112 (17), 77 (29), 69 (100), 68 (15), 67 (19), 41 (14).

Anal. Calcd for $C_{11}H_{14}Cl_2$: C, 60.85; H, 6.50; Cl, 32.65. Found: C, 60.5; H, 6.6; Cl, 32.8.

3-Chloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene. To a cooled suspension of 6.45 g (0.17 mol) of powdered lithium aluminum hydride in 150 ml of ether and 450 ml of tetrahydrofuran was added dropwise with stirring a solution of 20.6 g (0.095 mol) of 3,4-dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene obtained above over a period of 30 min. After the addition was completed, the reaction mixture was heated under gentle reflux for 22 hr. Any residual lithium aluminum hydride was decomposed by wet ether, and the resulting mixture was poured onto ice–water. The organic layer was separated, and the aqueous layer was, after acidification with 10% hydrochloric acid, extracted with ether (100 ml × 5). The combined organic layer and ether extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by fractional distillation gave 11.8 g (68%) of 3-chloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene: bp 77–79° (2 mm); $n^{25.6}$D 1.5223; ir 3045, 2935, 2855, 1640 (C=C), 1465, 1310, 1035, 957, 830, 680 cm^{-1}; ^{1}H nmr δ 0.8–2.8 (m, 14), 6.0 (d, 1, J = 7 Hz, C=CH); mass spectrum m/e (rel intensity) 182 (25), 115 (35), 114 (44), 113 (100), 112 (91), 79 (56), 77 (48), 69 (30), 67 (30), 41 (27).

Anal. Calcd for $C_{11}H_{15}Cl$: 73.32; H, 8.28; Cl, 19.40. Found: C, 72.5; H, 8.1; Cl, 19.4.

6,7-*exo*-Trimethylenebicyclo[3.2.1]octan-3-one (8). To 80 ml of 98% sulfuric acid cooled in an ice bath was added with efficient stirring 7.3 g (0.04 mol) of 3-chloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene in one portion, and the mixture was stirred at ambient temperature overnight. The reaction mixture was poured onto cracked ice and extracted three times each with 150 ml of ether. The ether solution was washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was distilled to give 3.6 g (55%) of 8: bp 75–77° (0.5 mm); $n^{25.6}$D 1.5031; ir 2945, 2850, 1710 (C=O), 1465, 1410, 1210, 1065, 825 cm^{-1}; ^{1}H nmr δ 0.7–2.5 (m); mass spectrum m/e (rel intensity) 164 (74, M$^+$), 121 (54), 120 (86), 95 (100), 79 (57), 68 (44), 67 (82), 41 (62).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.8; H, 10.2.

Ring Expansion of 5,6-*exo*-Trimethylenenorbornan-2-one. An Alternative Route to 8. To a cooled mixture of 30 g (0.2 mol) of 5,6-*exo*-trimethylenenorbornan-2-one,[23] 50 g (0.23 mol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, 60 ml of 95% ethanol, and 4 ml of water was added dropwise with gentle stirring a solution of 6 g of potassium hydroxide in 20 ml of 50% aqueous ethanol. The rate of addition was adjusted so that the temperature was maintained at 10–20°. After the addition was completed, the solution was stirred for an additional 30 min, acidified with 2 *N* hydrochloric acid, and extracted with petroleum ether. The organic layer was dried over anhydrous sodium sulfate, concentrated, and distilled. The fraction boiling at 77–79° (1 mm) gave 3.6 g (11%) of a mixture consisting of two components, as analyzed on the vpc. The first-eluted component (relative abundance 74%) was identical in all respects (ir and mass spectra and vpc retention times) with the authentic 8 obtained above.

The second component was assigned the structure of 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-2-one on the basis of the method of synthesis[22] and the following properties: ir 2945, 2855, 1710 (C=O), 1470, 1450, 1420, 1240, 1090, 1030, 915, 780 cm^{-1}; mass spectrum m/e (rel intensity) 164 (23, M$^+$), 136 (12), 123 (25), 120 (100), 107 (16), 93 (20), 92 (23), 91 (27), 80 (33), 79 (68), 77 (27), 67 (40), 53 (20).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.3; H, 10.1.

6,7-*exo*-Trimethylenebicyclo[3.2.1]octane (4). A mixture of 3.3 g (0.02 mol) of the ketone 8, 14 ml of 80% hydrazine hydrate, 11 g (0.2 mol) of potassium hydroxide, and 110 ml of diethylene glycol were heated under reflux for 3 hr. Water and excess hydrazine hydrate were then distilled off and the heating was continued under reflux (210°) for a further 5 hr.[24] After being cooled, the reaction mixture was poured onto cold water and extracted five times each with 100 ml of petroleum ether. The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was distilled to give 2.4 g (80%) of 4: bp 63–65° (2 mm); n^{22}D 1.4967; ir 2930, 2860, 1460, 1340, 1300, 1290, 1230, 1120, 1070, 970, 918, 870 cm^{-1}; ^{1}H mnr δ 0.9–2.3 (m); mass spectrum m/e (rel intensity) 150 (51, M$^+$), 135 (13), 108 (24), 93 (22), 91 (19), 79 (50), 67 (82), 55 (25), 53 (37), 41 (100); ^{13}C nmr (multiplicity, rel intensity) 20.2 (t, 1), 28.1 (t, 1), 32.5 (t, 2), 34.1 (t, 2), 34.8 (t, 1), 41.4 (d, 2), 47.9 (d, 2).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.9; H, 12.1.

Acid Catalyzed Rearrangement of Tricycloundecanes. A 20-ml two-necked erlenmeyer flask was equipped with a reflux condenser connected to a calcium chloride tube which was connected to a nitrogen cylinder through a T-shaped joint, one end of which was connected for nitrogen pressure release to a glass tube dipped by half an inch into liquid paraffin. After the flask was thoroughly flashed with nitrogen stream, an appropriate amount of the catalyst and 5 ml of methylene chloride were added. The mixture was stirred at ambient temperature until complete dissolution of the catalyst resulted; to the mixture was added with stirring a solution of 200 mg (1.33 mmol) of tricycloundecane in 5 ml of methylene chloride. The reaction was started and run under a nitrogen atmosphere at specified temperature, while aliquots (each 100 μ) were withdrawn and quenched by cold water. A part of the methylene chloride layer was taken and, without drying, subjected to vpc analysis. The amount of the catalyst used was 36 mg (0.267 mmol) for $AlCl_3$ and 200 mg (1.33 mmol) or 800 mg (5.32 mmol) for CF_3SO_3H. Reactions were run at ambient temperature when aluminum chloride was used, and under reflux when trifluoromethanesulfonic acid was used.

In case 95% sulfuric acid was used as catalyst, 5 g of sulfuric acid was placed in the flask to which was added 500 mg (3.33 mmol) of a tricycloundecane in 3.2 ml of solvent (carbon tetrachloride or methylene chloride). The reactions were run at ambient temperature. Interruption of stirring allowed separation of the organic layer, from which aliquots were withdrawn for vpc analysis after quenching by cold water.

Acknowledgment. We thank Dr. S. Sato, Director of Application Research Laboratories, Nippon Electric Varian Co., for the measurements of the ^{13}C nmr spectra.

Registry No.—**2,** 53432-45-4; **3,** 43000-53-9; **4,** 53495-28-6; **5,** 281-46-9; **8,** 53432-46-5; 5,6-*exo*-trimethylenenorborn-2-ene, 10466-50-9; ethyl trichloroacetate, 515-84-4; 3,4-dichloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene, 53432-47-6; 3-chloro-6,7-*exo*-trimethylenebicyclo[3.2.1]oct-2-ene, 53432-48-7; 5,6-*exo*-trimethylenenorbornan-2-one, 34748-64-6; *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, 80-11-5; 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-2-one, 53432-49-8.

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(5) The number of isomers containing neither three- nor four-membered ring amounted to 16 for $C_{10}H_{16}$[2,3] and 70 for $C_{11}H_{18}$: E. Osawa, to be published.
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Synthesis of 3-Keto-6-phenyl-8-methyl-9-oxa-$\Delta^{1,2}$-2-azabicyclo[4.3.0]nonane

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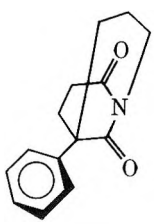
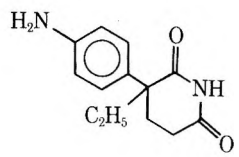
The synthesis and the study of the intramolecular cyclizations of ethyl 3-[3-phenyl-3-(2′-piperidonyl)]propionate (**3**), 2-(3-bromopropyl)-2-phenylglutarimide (**17**), and 2-(2-bromopropyl)-2-phenylglutarimide (**18**) are described. Although both N and O alkylations are possible, only the O-alkylated products were observed.

The synthesis of 5-phenyl-2,9-diketo-1-azabicyclo-[3.3.1]nonane (**1**), a bridged analog of aminoglutethimide (**2**), was undertaken in order to investigate the steric requirements of the antiepileptic action of drugs containing the ureide or imide moiety.



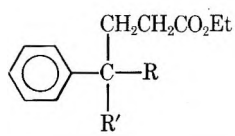
1



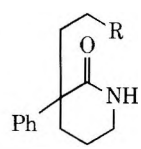
2

The initial approach to the synthesis of **1** involved the synthesis of ethyl 3-[3-phenyl-3-(2′-piperidonyl)]propionate (**3**). It was proposed that a base-catalyzed intramolecular attack by the amide nitrogen on the ester function would yield **1**.

Diethyl 2-phenylglutarate (**4**) was converted to diethyl 2-cyanoethyl-2-phenylglutarate (**5**) *via* cyanoethylation. Hydrogenation of **5** yielded the primary amine **6** which was converted without purification to the desired lactam ester **3**. Treatment of **3** with a variety of bases (sodium hydride, potassium *tert*-butoxide, thallous ethoxide, sodium hydroxide, and sodium ethoxide) in various solvent systems (dimethylformamide, dimethoxyethane, diethyl ether) failed to yield the desired bicyclic glutarimide **1**. The product isolated was identified as 3-[3-phenyl-3-(2′-piperidonyl)]propionic acid (**7**). This probably results from the initial

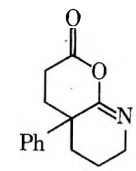


4, R′ = H; R = CO_2Et
5, R′ = CH_2CH_2CN; R = CO_2Et
6, R′ = $CH_2CH_2CH_2NH_2$; R = CO_2Et



3, R = CO_2Et
7, R = CO_2H

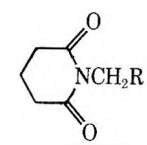
formation of **8** *via* intramolecular O-acylation followed by hydrolysis during isolation to give the acid **7**.



8

Attempts to cyclize compound **7** to the desired glutarimide **1** under various conditions (acetic anhydride, acetic anhydride and pyridine, thionyl chloride, dicyclohexylcarbodiimide, and polyphosphoric acid) yielded only starting material.

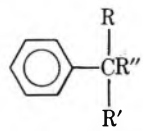
We previously reported[3] the light-catalyzed addition of hydrogen bromide to *N*-allylglutarimide (**9**) to yield *N*-(3-bromopropyl)glutarimide (**10**). If a small amount of acetic acid was added to the reaction *N*-(2-bromopropyl)glutarimide (**11**) was obtained. Attempts to cyclize **10** to the C-alkylated bicyclic system failed.



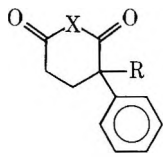
9, R = $CH{=}CH_2$
10, R = CH_2CH_2Br
11, R = $CHBrCH_3$

An alternate approach to the synthesis of **1** involved a base-catalyzed intramolecular alkylation of 2-(3-bromopropyl)-2-phenylglutarimide (**17**). We anticipated that the addition of a suitable base would lead to the abstraction of the relatively acidic imide proton and the resulting anion could afford nucleophilic displacement of the primary bromide of the propyl side chain to yield the desired compound **1**.

Phenylacetonitrile was allowed to react with allyl bromide and sodium hydride in dimethylformamide to yield 2-allylphenylacetonitrile (**12**). Cyanoethylation of **12** yielded 2-allyl-2-cyanoethylphenylacetonitrile (**13**) followed by hydrolysis to yield the diacid **14** which was converted to 2-allyl-2-phenylglutaric anhydride (**15**) with refluxing acetic



12, R = H; R′ = $CH_2CH{=}CH_2$; R″ = CN
13, R = CH_2CH_2CN; R′ = $CH_2CH{=}CH_2$; R″ = CN
14, R = $CH_2CH_2CO_2H$; R′ = $CH_2CH{=}CH_2$; R″ = CO_2H

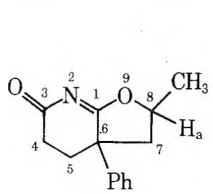


15, X = O; R = $CH_2CH{=}CH_2$
16, X = NH; R = $CH_2CH{=}CH_2$
17, X = NH; R = $CH_2CH_2CH_2Br$
18, X = NH; R = $CH_2CHBrCH_3$
22, X = NH; R = $CH_2CH_2CH_2OH$

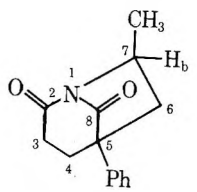
anhydride. Treatment of **15** with concentrated ammonium hydroxide afforded 2-allyl-2-phenylglutarimide (**16**) in good yield. Light-catalyzed addition of hydrogen bromide[3] to compound **16** gave 2-(3-bromopropyl)-2-phenylglutarimide (**17**). Addition of a trace of acetic acid or the use of water-saturated toluene as the solvent for the addition yielded 2-(2-bromopropyl)glutarimide (**18**).

Treatment of compound **18** with sodium hydride in dimethylformamide led to the formation of a product with an empirical formula consistent with either 3-keto-6-phenyl-8-methyl-9-oxa-$\Delta^{1,2}$-2-azabicyclo[4.3.0]nonane (**19**) or 2,8-diketo-5-phenyl-7-methyl-1-azabicyclo[3.2.1]octane (**20**).

The ir spectrum in chloroform showed strong absorptions at 1710 (C=O) and 1625 cm^{-1} (OC=N-) and in KBr at 1695 and 1615 cm^{-1}, respectively. The nmr spectrum in deuteriochloroform showed a three-proton doublet at δ 1.46, a complex multiplet of six protons between δ 1.80 and 2.90, and a one-proton multiplet centered at δ 4.50. Structure **20** was eliminated as a possibility on the basis of ir



19



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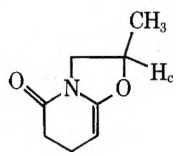
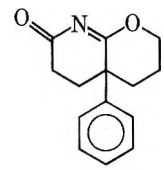


21

data (1625 cm^{-1}) which indicated the presence of a carbon–nitrogen double bond. In addition, in **20** the proton H_b would be expected to occur further upfield than δ 4.50. However, in **19** this would be a reasonable absorption for H_a. This assignment is supported by the report that the proton H_c in compound **21** also occurs at δ 4.50;[3] therefore, the ir and nmr data support structure **19**. Compound **19** slowly decomposes to a white gum if allowed to stand in the atmosphere.

In a similar manner, treatment of **17** with sodium hydride in benzene yielded a colorless gum which was purified using column chromatography. The ir spectrum showed absorptions at 3400 (-OH), 3210 (-NH), and 1680 cm^{-1} (C=O). The nmr spectrum in chloroform showed one exchangeable proton at δ 2.76 (-OH) and a broad singlet at δ 8.97 (imide H). On the basis of these data and elemental analysis the compound was identified as 2-phenyl-2-(3-hydroxypropyl)glutarimide (**22**). Isolation of this product suggests that base treatment leads to the formation of the O-alkylated bicyclic derivative **23** which is then opened during chromatography on the slightly acidic silica gel to yield the primary alcohol **22**.



23

Experimental Section[4]

Diethyl 2-Cyanoethyl-2-phenylglutarate (5). About 10 drops of a solution of acrylonitrile (5.76 g, 0.109 mol) in 25 ml of *tert*-butyl alcohol was added to a solution of diethyl 2-phenylglutarate (16.56 g, 0.062 mol) in 25 ml of *tert*- butyl alcohol. To this mixture was added sodium hydride (0.456 g of a 57% suspension, 0.019 mol) all at once. The remainder of the acrylonitrile solution was added dropwise with stirring and the resulting yellow reaction mixture was stirred at 25° for 8 hr. To this mixture was added 50 ml of H_2O, after which the solution was made acidic with 10% HCl, extracted with 3 × 100 ml of ethyl acetate, and dried ($MgSO_4$), and the solvents were removed to give a cloudy yellow, viscous oil. Distillation afforded the desired product: 12.10 g (0.038 mol, 62%); 165–170° (0.8 mm); nmr ($CDCl_3$, 1% TMS) δ 1.12–1.36 (t, 6, $-CH_2CH_3$), 2.20–2.48 (m, 8, $-CH_2CH_2-$), 3.46–3.96 (m, 4, $-OCH_2CH_3$), 7.28–7.40 (m, 5 H, aromatic); ir (neat) 2980, 3020, 2250, 1735, 1600, 1200 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.33; H, 7.51; N, 4.63.

Ethyl 3-[3-Phenyl-3-(2′-piperidonyl)]propionate (3). A solution of diethyl 2-cyanoethyl-2-phenylglutarate (5, 20.0 g, 0.063 mol) in 125 ml of glacial acetic acid was hydrogenated at 50 psi (initial pressure) over PtO_2 for 6 hr in a Parr shaker. The contents of the flask were filtered and the acetic acid was removed *in vacuo* to yield a clear viscous oil which was then heated to reflux in anhydrous toluene for 4 hr. The toluene was then removed *in vacuo* leaving a pale green oil which was chromatographed on 300 g of Brinkman silica gel (70–325 mesh) and eluted with ethyl acetate–benzene (2:1). The desired compound **3** was obtained as a clear colorless oil which crystallized immediately upon standing. Recrystallization from diethyl ether yielded 11.0 g (0.040 mol, 64%) of pure white needles: mp 90–91°; nmr ($CDCl_3$, 1% TMS) δ 1.10–1.30 (t, 3, $-CH_2CH_3$), 1.60–2.40 (m, 8, CH_2CH_2), 3.10–3.40 (br m, 2, $-CH_2NH$), 3.85–4.25 (q, 2, OCH_2CH_3), 6.60–6.80 (br s, 1, NH), 7.25 (s, 5, aromatic); ir (KBr) 3250, 2960, 1730, 1665 (shoulder), 1610, 1490, 1200 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.68; N, 5.08. Found: C, 70.03; H, 7.91; N, 5.38.

3-[3-Phenyl-3-(2′-piperidonyl)]propionic Acid (7). Ethyl 3-[3-phenyl-3-(2′-piperidonyl)]propionate (**3**) (2.0 g, 0.008 mol) was heated and stirred with 10 ml of 10% NaOH until the reaction mixture became homogeneous. The solution was extracted with ethyl acetate and the aqueous layer acidified with 10% HCl. The acidic solution was saturated with NaCl, extracted with 3 × 50 ml of ethyl acetate, and dried ($MgSO_4$), and the solvent was removed to yield 1.62 g (0.0064 mol, 80%) of a white solid. Recrystallization (ether–methanol) yielded colorless prisms: mp 158–160°; nmr (CD_3OD) δ 1.50–1.75 (m, 2, $-CH_2CH_2NH$), 1.85–2.20 (m, 6, $-CH_2CH_2COOH$ + $PhCCH_2$), 3.10–3.40 (m, 2, $-CH_2NH$), 7.40 (s, 5, aromatic); ir (KBr) 3300, 3100–2700, 1715, 1600, 1240 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.92; N, 5.66. Found: C, 67.82; H, 7.04; N, 5.93.

2-Allylphenylacetonitrile (12). To NaH (14.4 g, 0.6 mol) in 200 ml of dimethylformamide (DMF) was added phenylacetonitrile (70.3 g, 0.6 mol) in 100 ml of DMF dropwise while stirring the suspension. On addition the reaction mixture became deep red. After the addition the suspension was stirred for an additional 15 min. Allyl bromide (72.6 g, 0.6 mol) in 75 ml of DMF was then added dropwise after which the reaction mixture was refluxed for 5 hr. Crushed ice (800 g) was added, the mixture was extracted with 3 × 250 ml of ethyl acetate and dried ($MgSO_4$), and the solvent was removed to afford 96.4 g of a thick brown oil. Distillation yielded the desired product: 68.2 g (0.434 mol, 72.5%); bp 80–84° (1.0 mm) [lit.[5] bp 122–126° (12 mm)]; nmr ($CDCl_3$, 1% TMS) δ 2.50–2.76 (d, 2, $-CH_2CH{=}CH_2$), 3.50–4.00 (m, 1, benzylic H), 4.90–6.16 (m, 3, $-CH{=}CH_2$), 7.40 (s, 5, aromatic); ir (neat) 3110, 3100, 3060, 2260, 1650, 1610, 1450, 990, 930 cm^{-1}.

2-Allyl-2-cyanoethylphenylacetonitrile (13). Sodium hydride (0.5 g) was dissolved in 200 ml of anhydrous *tert*-butyl alcohol and to this was added 2-allylphenylacetonitrile (**12**, 28.2 g,

0.179 mol) in 50 ml of *tert*-butyl alcohol. Immediately upon addition the reaction mixture darkened. Acrylonitrile (19.0 g, 0.36 mol) in 100 ml of *tert*-butyl alcohol was then added slowly, dropwise, with stirring. The reaction mixture became exothermic and was maintained at 40–50° with a water bath for 2 hr. The reaction mixture was then made acidic with 50 ml of 10% HCl and diluted with 250 ml of H_2O. The aqueous solution was extracted with 3 × 250 ml of ethyl acetate and dried ($MgSO_4$), and the solvent was removed to yield a viscous brown oil. This oil was distilled to yield 13.3 g (0.063 mol, 35%) of the desired product: bp 142–150° (0.4 mm) [lit.[5] bp 200–202° (18 mm)]; nmr ($CDCl_3$, 1% TMS) δ 2.24–2.60 (m, 4, $-CH_2CH_2CN$), 2.68–2.88 (d, 2, $-CH_2CH{=}CH_2$), 5.00–L.10 (m, 3, $CH_2CH{=}CH_2$), 7.50 (s, 5, aromatic); ir (neat) 3120, 3100, 3010, 3060, 2970, 1650, 1610, 990, 935, 760, 690 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.18; H, 6.49; N, 13.14.

2-Allyl-2-phenylglutaric Anhydride (15). To 50 ml of an aqueous solution of KOH (10.6 g, 0.2 mol) was added 10.0 g (0.047 mol) of 2-allyl-2-cyanoethylphenylacetonitrile (**13**). The reaction mixture was refluxed 48 hr, acidified with 10% HCl, extracted with 3 × 100 ml of ethyl acetate, and dried ($MgSO_4$), and the solvent was removed to give 11.6 g of a pale yellow oil (98.3%). This oil was refluxed in 25 ml of acetic anhydride for 2 hr. The mixture was cooled and the excess volatile reactants were removed *in vacuo* to give a dark, viscous, orange oil. The oil was dissolved in ethyl acetate and decolorized with charcoal. Filtration and distillation yielded 8.62 g (0.037 mol, 80%) of the desired product: bp 142–144° (0.4 mm); nmr ($CDCl_3$, 1% TMS) δ 2.30–2.42 (m, 2, $-CH_2CH{=}CH_2$), 2.52–2.82 (m, 4, $-CH_2CH_2-$), 4.90–6.00 (m, 3, $-CH_2CH{=}CH_2$), 7.25–7.40 (m, 5, aromatic); ir (neat) 3100, 3055, 2960, 1810, 1765, 1640, 1060, 915, 750, 685 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.14. Found: C, 73.12; H, 6.28.

2-Allyl-2-phenylglutarimide (16). An aqueous solution of NH_4OH (58% solution, 18.3 g, 0.52 mol) and 30.0 g (0.13 mol) of 2-allyl-2-phenylglutaric anhydride (**15**) were slowly heated to reflux. The water was allowed to distil and heating was continued until the initially clear light yellow solution began to darken (*ca.* 3 hr). The reaction mixture was cooled to 25° to yield a thick tarry material. This material was distilled to give 23.0 g (0.098 mol, 76%) of a clear, viscous oil: bp 158–160° (0.2 mm) [lit.[5] bp 191–193° (5 mm)]; nmr ($CDCl_3$, 1% TMS) δ 2.20–2.80 (m, 6, $CH_2CH{=}CH_2$ + $-CH_2CH_2$), 4.80–5.90 (m, 3, $-CH_2CH_2$), 7.20 (s, 5, aromatic), 9.20 (s, 1, imide H); ir ($CHCl_3$) 3400, 1710, 1645, 1175, 915 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.10. Found: C, 73.43; H, 6.81; N, 6.03.

2-(3-Bromopropyl)-2-phenylglutarimide (17). Into a solution of 100 ml of anhydrous toluene and 0.25 g of benzoyl peroxide was placed 1.00 g (0.004 mol) of 2-allyl-2-phenylglutarimide. The reaction mixture was irradiated with a Westinghouse sunlamp (275 W, 110–125 V) while HBr was bubbled through the solution. Irradiation and HBr addition was continued for 15 min after which time the solution was purged with N_2. The toluene was removed leaving a thick orange oil which was dissolved in 50 ml of ether and placed in a refrigerator. Crystallization occurred on standing overnight to yield 1.10 g (0.0035 mol, 82.5%) of a solid. Recrystallization (ether) gave white needles: mp 95–97°; nmr ($CDCl_3$, 1% TMS) δ 1.65–2.60 (m, 8, ring H's + $-CH_2CH_2CH_2Br$), 3.18–3.40 (t, 2, $-CH_2Br$), 7.30 (s, 5, aromatic), 9.60 (s, 1, imide H); ir ($CHCl_3$) 3390, 2980, 1700–1720, 1340, 1260, 1170 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}NO_2Br$: C, 54.20; H, 5.19; N, 4.51. Found: C, 54.40; H, 5.30; N, 4.78.

2-(2-Bromopropyl)-2-phenylglutarimide (18). If wet toluene was used in the procedure for **17**, compound **18** was obtained. Removal of the toluene after the addition of HBr to 2.30 g (0.01 mol) of 2-allyl-2-phenylglutarimide afforded a viscous brown oil which was dissolved in hot ethyl acetate. On cooling, a light-brown solid formed which was filtered, washed with cold ehher, and dried to give 2.75 g (0.009 mol, 90%) of **18**. Recrystallization (ether–acetone) produced white crystals: mp 159–160°; nmr ($CDCl_3$, 1% TMS) δ 1.50–1.60 (d, 3, J = 6 Hz, $-HCBrCH_3$), 2.10–2.80 (m, 6, ring H's + $-CH_2CHBr-$), 3.90–4.05 (m, 1, $-CH_2CHBrCH_3$), 7.20 (s, 5, aromatic), 10.40 (s, 1, imide H); ir (KBr) 3210, 1720, 1690, 1360, 1260, 1200, 1180 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}NO_2Br$: C, 54.20; H, 5.19; N, 4.51. Found: C, 54.26; H, 5.07; N, 4.80.

Reaction of 2-Phenyl-2-(3-bromopropyl)glutarimide with Sodium Hydride. In 125 ml of anhydrous benzene was dissolved 2.0 g (0.0065 mol) of 2-phenyl-2-(3-bromopropyl)glutarimide and to this was added 0.24 g (0.01 mol) of NaH [washed free of mineral oil with petroleum ether (bp 60–68°)] all at once. Immediately upon addition, H_2 began to evolve and the reaction mixture was allowed to stir at room temperature for 24 hr. The reaction mixture was then filtered (solid identified as NaBr) and the solvent removed to yield a viscous orange-brown oil. This oil was chromatographed on 50 g of Brinkman silica gel (70–325 mesh) and eluted with ethyl acetate–benzene (1:1). Chromatography yielded 1.10 g (0.0045 mol, 69%) of 2-phenyl-2-(3-hydroxypropyl)glutarimide (**22**), a low-melting, hygroscopic white solid: mp 76–78°; nmr ($CDCl_3$, 1% TMS) δ 1.13–2.50 (m, 8, CH_2CH_2), 2.76 (br s, 1, disappears with addition of D_2O, OH), 3.43–3.63 (t, 2), 7.33 (s, 5, aromatic), 8.80–9.13 (brs, 1, imide H); ir (KBr) 3400, 3210, 1680, 1340, 1175 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.92; N, 5.66. Found: C, 67.79; H, 6.79; N, 5.55.

3-Keto-6-phenyl-8-methyl-9-oxa-$\Delta^{1,2}$-2-azabicyclo[4.3.0]-nonane (19). In 30 ml of anhydrous DMF was placed 1.55 g (0.005 mol) of 2-(2-bromopropyl)-2-phenylglutarimide. Directly to this mixture was added 0.21 g (57% suspension, 0.005 mol) of NaH and the solution was stirred for 24 hr. The DMF was then removed *in vacuo* to leave a tan residue. This was partially dissolved in H_2O and immediately extracted with ether (3 × 50 ml). The ethereal extract was dried (Na_2SO_4) and the solvent removed to yield a white solid (0.52 g, 0.0023 mol, 46%). Recrystallization (ether) yielded thin colorless needles: mp 164–166°; nmr ($CDCl_3$, 1% TMS) δ 1.45–1.55 [d, 3, J = 6 Hz, $-OC(CH)CH_3$], 1.85–2.90 (m, 6, CH_2), 4.30–4.85 [m, 1, $-OC(CH_3)H$], 7.30 (s, 5, aromatic); ir ($CHCl_3$) 3030, 2960, 1710, 1625, 1230, 950 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.10. Found: C, 73.50; H, 6.76; N, 6.15.

Acknowledgments. The authors wish to acknowledge the support of this work by the National Institutes of Health Grant GM 01341 and by the National Science Foundation Undergraduate Participation Grant GY 19874.

Registry No.—**3,** 53370-32-4; **4,** 53370-33-5; **5,** 53370-34-6; **7,** 53370-35-7; **12,** 5558-87-2; **13;** 53370-36-8; **15,** 53370-37-9; **16,** 53370-38-0; **17,** 53370-39-1; **18,** 53370-40-4; **19,** 53370-41-5; **22,** 53370-42-6; acrylonitrile, 107-13-1; phenylacetonitrile, 140-29-4; allyl bromide, 106-95-6.

References and Notes

(1) Deceased July 14, 1974.
(2) Taken in part from the dissertation presented by P. J. Wirth, Aug 1974, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.
(3) E. E. Smissman and J. W. Ayres, *J. Org. Chem.*, **37**, 1092 (1972).
(4) Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. Nuclear magnetic resonance spectra were obtained using Varian A-60A and T-60 spectrometers. Elemental analyses were determined on a Hewlett-Packard 185 C, H, N analyzer at the University of Kansas.
(5) M. P. Mertes and C. O. Wilson, *J. Amer. Pharm. Ass.*, **47**, 882 (1958).

The Isomeric *trans,trans*-Bicyclo[6.1.0]non-4-enes[1,2]

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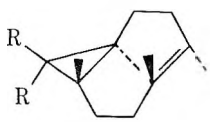
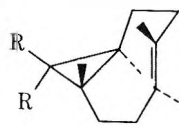
cis,trans-Bicyclo[6.1.0]non-4-enes have been prepared *via* two different routes and photoisomerized to the "parallel" and "perpendicular" isomers of *trans,trans*-bicyclo[6.1.0]non-4-enes. Structures for these isomers were confirmed and assigned by chemical and spectral means. Most noteworthy properties of these isomers include distortion from true perpendicularity in the "perpendicular" isomer and apparent severe distortion from planarity of the "parallel" isomer's double bond. The latter property apparently facilitates a remarkable thermal cis–trans isomerization of an isolated double bond. A comparison of the ultraviolet spectra of the two isomers also supports the postulated interaction between the cyclopropane and the π bond. Other chemistry of these isomers is discussed.

The consequences of cyclopropane ring interactions with proximate reacting centers and unsaturated groups have evoked considerable experimental and theoretical study. In an attempt to probe yet another facet of such interactions, we undertook syntheses of the "parallel" (**1**) and "perpendicular" (**2**) *trans,trans*-bicyclo[6.1.0]non-4-enes. Molecular models of these two isomers showed that the π and the transannular cyclopropane bonds possessed a common axis and that these two bonds were in extremely close proximity to each other. Thus, as viewed from the perspective offered by molecular models, the structural features of these isomers might provide a unique opportunity to study interactions between cyclopropanes and alkenes (as well as other alkene derived products) as a function of two closely related and possibly optimum geometries.

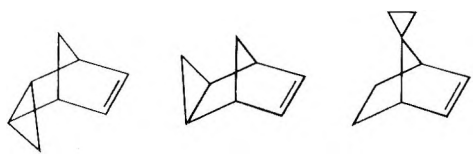


1a, R = Cl
b, R = H



2a, R = Cl
b, R = H

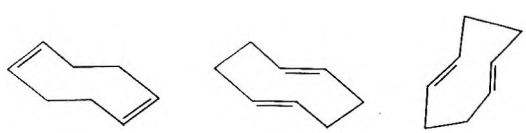
Effects of geometry and distance have been noted on through-space cyclopropane–alkene interactions in other systems (*e.g.*, **3**–**5**).[3] In contrast to these previous studies,



3 **4** **5**

the interfunctional distances of **1** and **2** appeared to be significantly shorter. In addition, the parallel orientation of the p orbitals and the cyclopropane ring in **1** forces maximum possible interactions between these two structural entities.

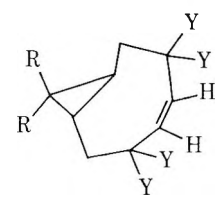
A hint at the potential importance of such orientation–distance factors can be found in a previous study by Cope and Whitesides.[4] In this study, photochemical isomerization of the Cu_2Cl_2 complex of *cis,cis*-1,5-cyclooctadiene (**6**)



6 **7** **8**

formed a product in low (1–2%) yield which was assigned the 1,5-*trans,trans*-cyclooctadiene structure. Although these authors were unable to determine whether their product was **7**, **8**, or a mixture of both, they did note chemical instability and ultraviolet spectral properties apparently indicative of transannular interactions. By contrast, **6** is relatively unremarkable in its chemical reactivity.

Synthesis. Cyclization Approach. Since the *trans*-alkene moiety was expected to be the most reactive component of the desired structures, we focused on synthetic approaches in which its formation would be the final step. Although an isomerization of the cis isomer **9** appeared to be

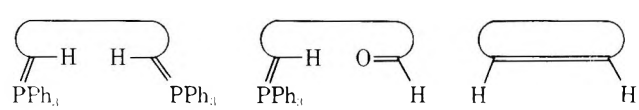


9a, R = Cl; Y = H
b, R = Cl; Y = D
c, R = H; Y = H

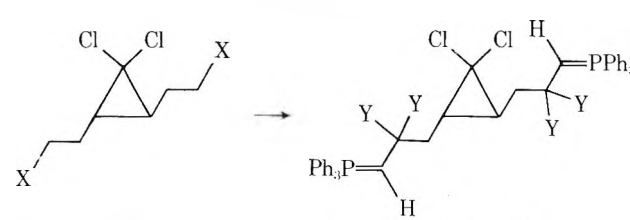
the simplest approach, the low yields obtained by Cope and Whitesides in the synthesis of *trans,trans*-1,5-cyclooctadiene (**6** or **7**) made this approach initially less desirable.

An apparently attractive alternative was found in an adaptation of Bestman's symmetrical alkene synthesis.[5] This synthesis involves the oxidation of diphosphonium ylides by molecular oxygen (Chart I). Under favorable circumstances the ylide–aldehyde reacts intramolecularly more rapidly than further oxidation or intermolecular reaction can occur. The appropriate precursor **13e** was prepared in a number of steps (Scheme I) from **13b**. Compound **13b** was

Chart I



Scheme I

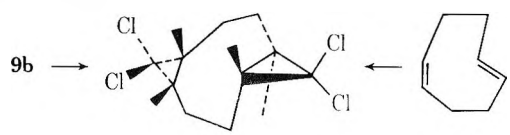


13a, X = $CO_2C(CH_3)_3$
b, X = CO_2CH_3
c, X = CH_2OH
d, X = CH_2OTs
e, X = CH_2I
f, X = $CH_2P^+(Ph)_3X^-$
g, X = CO_2H

11a, Y = H
b, Y = D

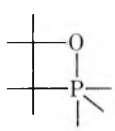
in turn synthesized by addition of dichlorocarbene to the corresponding trans unsaturated ester.[6] Simultaneous high dilution addition of **13e** and 2 equiv of sodium methylsulfinyl methide to oxygenated dimethyl sulfoxide yielded a single product of the desired molecular weight in 22% yield.[7] The general structure of this product was established *via* ozonolysis to **13g.** This ozonolysis product was identical in all respects with a product obtained by chromic acid oxidation of **13c.**

In order to establish the stereochemistry of the cyclization product, **13a**[6] was deuterated by exchange with $(CH_3)_3COD$–$(CH_3)_3COK$. This product was transesterified, the tetradeuterio dimethyl ester was then carried through steps outlined in Scheme I, and the resultant tetradeuterio diylide **14b** was cyclized to **9b** as described above. A ^{13}C satellite nmr spectrum was obtained on the olefinic protons of this product and this spectrum revealed a coupling constant $J_{C^{13}\text{-}H,C^{12}\text{-}H}$ of 11.5 Hz. Comparison of this coupling constant with coupling constants obtained for other normal and medium-sized rings[8] established that the cyclization product had the cis stereochemistry about the double bond. Chemical confirmation of this assignment was obtained from the observed total unreactivity of the cyclization product toward 1,3-dipoles such as phenyl azide.[9] Final proof of structure was obtained by the reaction of the cyclization product **9b** with 1 mol of dichlorocarbene to give **15.** This product was identical in all respects with one prepared directly from **16.**



15 16

Formation of alkenes *via* the Wittig reaction ordinarily yields a stereochemical mixture.[10] Although it is difficult to predict the composition of such mixtures, the trans isomer is most frequently the major product. To the extent, however, that stereochemistry is governed by angle stain and/or steric crowding in the transition state (or intermediate) **17,** molecular models seemed to indicate a preference for



17

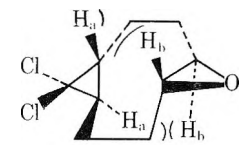
the desired trans isomers. From our observed results it is clear that these factors do not dictate stereoselectivity in this cyclization. This result is all the more interesting in view of the fact that a mixture of **1** and **2** (*vide infra*) was unaltered in composition (although partially destroyed) when subjected to the cyclization reaction conditions.

Compound **9** could be prepared more efficiently by controlled selective addition to the more reactive trans double bond of **16.** Thus, addition of dichlorocarbene or diazomethane (followed by photolysis) yielded **9a** and **9c,**[11] respectively. The more cumbersome oxidative cyclization route did make **9b** available and this compound proved to be exceptionally useful, as will be described subsequently.

Isomerization Approach. Since the results of the oxidative cyclization suggested that any nonstereospecific alkene formation might also yield **9,** we reconsidered the possibility that **9** could be photochemically isomerized to the desired structures **1** and **2.** The two major problems with this approach were the prospects for low yields (*vide supra*) and the lack of a stable complex between **9** and cuprous chloride. After some experimentation it was found that a preformed cuprous chloride complex was unnecessary. Observations concerning this procedure and its application to the synthesis of *trans*-cyclooctene have already been published.[12] In brief, the cuprous chloride functions both as a sensitizer for the isomerization and also displaces the equilibrium by virtue of the greater stability of the complex with the more strained *trans*-alkene.

Irradiation of **9a** and cuprous chloride at 2537 Å in hexane for 27 hr produced a mixture which had three components with similar glc retention times. Extraction of this mixture with aqueous silver nitrate left the major component behind in the organic phase. This component was shown to be identical with starting material **9a.** Addition of aqueous ammonia to the silver nitrate solution liberated the two minor products in 43% yield. These two minor products were present in a 5 to 1 ratio before and after the silver nitrate extractions. They were separated by preparative glc and shown by mass spectroscopy to be isomeric with **9a.** Gross structure and the location of the double bond were confirmed by ozonolysis. In a similar manner isomerization of **9c** gave a mixture of two silver nitrate soluble isomers in 20% yield. These isomers which were present in a 7 to 1 ratio were also separable by preparative glc.

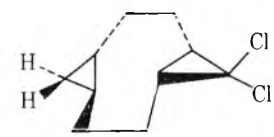
In order to distinguish between **1** and **2,** the major isomer from **9a** was converted to its epoxide and submitted for X-ray diffraction analysis.[13] This analysis established structure **18** for the epoxide and proved that the predominent



18

isomer was **2a.** The most interesting structural feature revealed by the X-ray analysis is the deviation from true perpendicularity of the two three-membered rings. This deviation apparently results from minimization of transannular repulsions between H_a and H_b. The resultant angle between the planes of the two three-membered rings is thus 70.3° instead of 90°. It is likely that similar factors pertain to **2.**[14]

Addition of the Simmons–Smith reagent converted **2a** to **19.** The same product was obtained by addition of dichloro-



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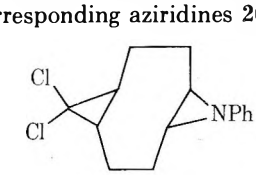
carbene to the major product from **9c.** In this way both major products were assigned the "perpendicular" structure and the "parallel" structure was attributed to the minor isomers.

Chemical and Spectral Properties. The fact that **1** and **2** (in contrast to **9**) are soluble in aqueous silver nitrate confirms the presence of strained trans double bonds in both of these compounds.[15] Also, in another reaction characteristic of olefinic strain, both **1** and **2** reacted extremely rapidly with phenyl azide.[9] The resultant triazolines were not characterized but photochemically converted to the corresponding aziridines **20** and **21.** Further important in-



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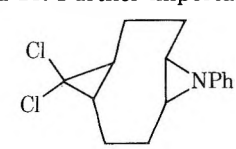

21

EXPERIMENTAL SECTION

General Methods: Unless otherwise noted all melting points were determined in glass capillaries and are uncorrected. Liquid samples of less than 6 g were generally distilled using a hot air bath and the boiling point reported was the temperature of the air bath. Irradiations at 2537 Å were done in a Southern New England Ultraviolet Co. (Middletown, Conn.) "Rayonet" Model RS Preparative Photochemical Reactor. Irradiation at longer wavelengths was carried out using a Hanovia 550w medium pressure quartz mercury arc lamp equipped with a water-cooled Pyrex immersion well (Ace Glass Co., Vineland, N.J.). Routine infrared spectra were measured with a Perkin-Elmer (Norwalk, Conn.) Model 137 "Infracord" instrument and ultraviolet spectra were measured using a Cary Model 15 recording spectrophotometer (Applied Physics Corp., Monrovia, California). Vacuum ultraviolet spectra were recorded on a MacPherson Model 665 (MacPherson Instrument Co., Acton, Massachusetts) recording spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian Associates (Palo Alto, California) type A-60 instrument. Carbon-13 Satellite Spectra were recorded using a Varian Associates type XL-100 instrument. Chemical shifts (δ) are expressed in ppm using tetramethylsilane as an internal standard. Preparative gas chromatographic separations were performed on a Hewlett-Packard (Palo Alto, California) Model 700 gas chromatograph using the Model 5795 A preparative attachment. Analytical gas chromatographs were obtained on a Varian Associates (Palo Alto, California) Aerograph Hy-Fi Model 600-D analytical gas chromatograph using 6' x 1/8" columns. Peak areas were measured by disc integration. Mass spectra were recorded on a Perkin-Elmer Hitachi (Norwalk, Conn.) Model RMU-6E mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc. (Knoxville, Tennessee) and by Atlantic Microlabs, Inc. (Atlanta, Georgia).

3,3-Dichloro-trans-1,2-cyclopropane Dipropionic Acid Dimethyl Ester (13b)

A solution of 31.5 g (0.157 mole) of dimethyl trans-4-octene-1,8-dioate[6b] in 100 ml of 1,2-dimethoxyethane (glyme), which had been dried over molecular sieves, and 29.0 g (0.157 mole) of sodium trichloroacetate was refluxed for 12.0 hours. A slow addition of crystalline sodium trichloroacetate from a bottle attached to the apparatus was then begun. The liberated CO_2 was allowed to vent from a $CaCl_2$ drying tube attached to the top of the condenser. The reaction was monitored by gas chromatography (SE-30) and required 5 days for completion. At this point, the addition was 96% complete and a 16-fold molar excess of sodium trichloroacetate had been used. Workup consisted of diluting the very black and viscous reaction mixture with ether, filtering off the precipitated NaCl, and evaporating the filtrate down to a very black oil. Analysis of this oil by gas chromatography showed only product and a small amount of starting material as the only volatile materials. Vacuum distillation of this oil at 135°/1.5 mm gave 31.8 g (76%) of product. Triturating the residue in boiling acetone, followed by filtration through Florex, evaporation of the filtrate to an oil and vacuum distillation of the oil gave an additional 9.1 g of material. A total yield of 41.9 g (94%) of dichloro cyclopropane 13b was thus obtained. $\delta^{tms}_{CDCl_3}$ 3.75 (singlet, 6H); 2.52 (multiplet, 4H); 1.93 (multiplet, 4H); and 1.37 (multiplet, 2H).

3,3-Dichloro-trans-1,2-di(3-hydroxypropyl)Cyclopropane (13c)

A mixture of 22.4 g (0.558 mole) of $LiAlH_4$, 41.7 g (0.147 mole) of 13b and 400 ml of anhydrous ether was refluxed for 5 hours. The mixture was then cooled in an ice bath, stirred, and to it was cautiously added 22.5 ml of H_2O, 22.5 ml of 15% aqueous NaOH, followed by 67.5 ml more H_2O. The mixture was then allowed to stir in the ice bath for 0.5 additional hours. The inorganic salts were then filtered off, the filtrate dried over $MgSO_4$ and evaporated to give a quantitative yield of the diol 13c (33 g). $\delta^{tms}_{CDCl_3}$ 3.70 (multiplet, 4H); 3.42 (singlet, 2H); 1.71 (multiplet, 8H); and 1.18 (multiplet, 2H). Washing the $CDCl_3$ solution of this material once with D_2O completely eliminated the singlet at 3.42δ.

3,3-Dichloro-trans-1,2-cyclopropane Dipropionic Acid (13g)

A chromic acid oxidizing solution[21] was prepared by adding 2.3 ml (0.044 mole) of conc. H_2SO_4 to 2.67 g (0.027 mole) of chromium trioxide and diluting the resulting mixture to a volume of 10 ml with H_2O. A solution of 0.55 g (0.0024 mole) of diol 13c in 40 ml of acetone was then prepared, stirred and cooled in an ice bath. To the solution was then added, under a N_2 atmosphere, a sufficient quantity of the oxidizing solution (ca. 3.5 ml) to cause a persistence of yellow color. The mixture was then stirred at room temperature for 20 hours. Methanol (0.5 ml) was then added, followed by filtration and evaporation. Ether was added to the residue and then saturated aqueous NaCl. The mixture was shaken and separated. The ether layer was dried over $MgSO_4$ and evaporated to an oil. The oil was picked up in ether-petroleum ether and crystallized at -20° to give material (13g) melting at 100-101.5°. One recrystallization gave an analytical sample (mp 101-102°). $\delta^{tms}_{CDCl_3}$ 11.3 (singlet, 2H); 2.56 (triplet, 4H); 1.85 (multiplet, 4H); and 1.30 (multiplet, 2H). ir: 3,000 (broad); 1,705; 1,415; 1,270; 1,218; 919 and 824 cm^{-1}.

Analysis: Calcd. for $C_9H_{12}O_4Cl_2$: C, 42.37; H, 4.74. Found: C, 42.59; H, 4.84.

3,3-Dichloro-trans-1,2-di(3-tosylpropyl)Cyclopropane (13d)

This compound was first prepared by dissolving 5.8 g (0.025 mole) of diol 13c in 125 ml pyridine (distilled over CaH_2) followed by the addition of 19.1 g (0.100 mole) of p-toluenesulfonyl chloride (recrystallized from $CHCl_3$ petroleum ether). The flask was then stoppered and cooled to -20° for 43 hours. The mixture was then added to 500 ml of rapidly stirred ice and H_2O. After 15 minutes the mixture was then extracted 3 times with ether. The ether layers were washed twice with cold 1:1 HCl and once with H_2O, dried over $MgSO_4$, clarified with Norit and evaporated. The residue was picked up in 60 ml ether and crystallized (mp 53-54°) at -78° in a dry ice-acetone bath. Two crops afforded 8.15 g (62%) of ditosylate 13d. Attempts to scale up this reaction, however, resulted in a marked decrease in yield. $\delta^{tms}_{CDCl_3}$ 7.25-7.95 (quartet, 8H); 4.08 (triplet, 4H); 2.46 (singlet, 6H); 1.67 (multiplet, 8H) and 1.01 (multiplet, 2H).

Analysis: Calcd. for $C_{23}H_{28}O_6S_2Cl_2$: C, 51.59; H, 5.27; Cl, 13.24. Found: C, 51.32; H, 5.43; Cl, 13.42.

A more efficient large-scale preparation consisted of dissolving 20.0 g (0.088 mole) diol 13c in 400 ml benzene followed by the addition of 12.5 g (0.65 mole) of sodium hydride (prepared from 25.0 g of the 50% dispersion by three washings with pentane). The whole mixture was cooled in an ice bath (in order to keep foaming down to a minimum), and was mechanically stirred for about 10 minutes. A solution of 38.0 g (0.18 mole) of freshly purified p-toluene sulfonyl chloride dissolved in 100 ml benzene was added dropwise over a period of 45 min. Once addition was complete, the ice bath was removed and the mixture allowed to stir at room temperature for 18 hours. The mixture was then cooled in an ice bath and water was very cautiously added to the stirred mixture. Once the excess NaH was destroyed, the mixture was washed three times with water, dried over $MgSO_4$ and evaporated to an oil (37.0 g, 90%) which could not be crystallized. This oil, however, gave an nmr spectrum identical to the material prepared earlier and appeared quite free from impurities and, hence, was used without further purification.

3,3-Dichloro-trans-1,2-di-(3-iodopropyl)Cyclopropane (13e)

This compound was prepared by dissolving 30.2 g (0.19 mole) of NaI in 200 ml of acetone and adding this solution to 25.5 g (0.048 mole) of ditosylate 13d dissolved in 100 ml of acetone. The flask was then swirled to give solution, flushed with nitrogen, stoppered and placed in the dark at room temperature for 42 hours. The solvent was then evaporated and to the mushy crystalline residue was added first ether and then water. The mixture was shaken and then separated. The aqueous layer was extracted twice more with ether, the ether solutions combined, dried over $MgSO_4$ and evaporated to an oil (21.0 g, 99%) which could not be crystallized. $\delta^{tms}_{CDCl_3}$ 3.25 (triplet, 4H); 1.45-2.3 (multiplet, 8H); 1.20 (multiplet, 2H).

3,3-Dichloro-trans-1,2-di-(3-triphenylphosphonio-propyl)-cyclopropyl Diiodide (13f; X=Cl)

The reaction was carried out by refluxing a mixture of 37.0 g (0.141 mole) of triphenylphosphine, 21.0 g (0.046 mole) of the diiodide (13e) and 100 ml of acetonitrile for 31.5 hours. The mixture was then evaporated until the oily residue began to foam. The foaming oil was then dissolved in acetone and refluxed. After approximately one hour a crystalline precipitate appeared which was filtered off. Another crop obtained in this manner from the filtrate afforded a total of 40.3 g (91%) of crystalline phosphonium salt mp 215-217 (dec.). $\delta^{tms}_{CDCl_3}$ 7.80 (multiplet, 30H); 3.70 (very broad singlet, 4H); 1.50-2.31 broad multiplet, 10H).

Analysis: Calcd. for $C_{45}H_{44}P_2Cl_2I_2$: C, 55.64; H, 4.57. Found: C, 55.86; H, 4.69.

This material was then converted to the corresponding dichloride salt (13f; X=Cl) by eluting it with ethanol through a column containing Dowex 21K chloride anion exchange resin. Recovery of material was quantitative and testing the product with dilute aqueous $AgNO_3$ indicated that the exchange was >97% complete. The evaporation of the ethanol solvent left an oil which foamed lightly. Pumping on the oil at high vacuum (0.02 mm) converted it into a very hygroscopic solid amorphous mass. Although it was used at that point without further purification, extreme care had to be used in handling it due to its extremely hygroscopic nature.

9,9-Dichloro-trans-bicyclo [6.1.0] non-cis-4-ene (9a)

A 0.27 N solution of sodium methylsulfinyl methide[22] was prepared and filtered through sintered glass under vacuum in order to obtain a clear solution.

The following apparatus for oxidative cyclization was constructed: a 250 ml 3-neck RB flask was fitted with two Hershberg dropping funnels and an oxygen bubbler. A stopcock was attached to the pressure equalization tube on each of the dropping funnels. The oxygen bubbler consisted of a straight tube with a sintered glass (medium fritted) disc attached to the end through which oxygen could be admitted. Attached to the upper part of the joint holding the tube was a vent leading to a mercury bubbler. Addition to the dropping funnels were made via syringe and serum stopper; and when the funnels were filled, the stopcocks on the pressure equalization tubes were closed and the reservoirs connected to a balloon filled with argon. Magnetic stirring was used and the reaction flask was heated by means of an oil bath. Once the apparatus was assembled it was twice evacuated to 0.4 mm, flamed and filled with argon.

To the reaction flask was then added via syringe, 20 ml of dimethyl sulfoxide (dried over calcium hydride for 5 days) and the flask heated to 50°. One dropping funnel was then filled with a solution of 2.42 g (3.1 mmoles) of the diphosphonium chloride (13f; X=Cl) in 30 ml of dried dimethyl sulfoxide. The other funnel was then charged with 30 ml of the 0.27 N solution of sodium methylsulfinyl methide prepared above. Stirring was then started and oxygen (passed first through conc. H_2SO_4 and then KOH pellets) was allowed to bubble at a moderate rate through the stirring liquid. Dropwise addition from both funnels was then started and regulated so that at all times an equal quantity of liquid was being added from each funnel with the rate of addition remaining constant. Approximately 30 minutes were required for complete addition, after which oxygen was allowed to continue bubbling through the stirring dark red mixture for an additional 15 minutes. Workup consisted of diluting the reaction mixture 3-fold with water and extracting the resulting mixture 3 times with pentane. The pentane extracts were combined, dried over $MgSO_4$, and concentrated to ca. 15 ml by distillation using a wire gauze column. The concentrated solution was then filtered and evaporated at 0° to an oily residue. The residue was then distilled (60°/0.2 mm) to give 130 mg (22%) of a very pungent oil (9a). Analysis by gas chromatography (Fluorosilicone, QF-1) showed this oil to consist of a single product. $\delta^{tms}_{CCl_4}$ 5.65 (multiplet, 2H); 2.19 (multiplet, 6H); and 1.21 (broad singlet, 4H). Mass spectrum, 191 m/e (M^+).

Analysis: Calcd. for $C_9H_{12}Cl_2$: C, 56.56; H, 6.33. Found: C, 56.58; H, 6.46.

di-t-butyl 2,2,7,7-Tetradeutero-trans-4-octene-1,8-dioate

To a solution of 21.2 g (0.025 mole) of di-t-butyl trans-4-octene-1,8-dioate in 75 ml of deuterated t-butanol was added ca. 0.5 g potassium-t-butoxide. The magnetically stirred mixture was then heated to 60° in an oil bath for 21 hours. After evaporation of the solvent to ca. 25% of its original volume, ether was added, followed by filtration using $MgSO_4$ as a filter-aid. The filtrate was then evaporated to dryness whereupon crystallization commenced. The crystals were then dried under vacuum (0.05 mm) for 4 hours. Recycling the material three more times using 50 ml, 40 ml and 35 ml deuterated-t-butanol, respectively, as solvent afforded a quantitative yield of the diester in 96% isotopic purity (nmr). $\delta^{tms}_{CCl_4}$ 5.41 (multiplet, 2H); 2.20 (triplet, J=1Hz, 4H); 1.39 (singlet, 18H).

9,9-Dichloro-3,3,6,6-tetradeutero-trans-bicyclo [6.1.0] non-cis-4-ene (9b)

Starting with 20.0 g (0.07 mole) of di-t-butyl 2,2,7,7-tetradeutero-trans-4-octene-1,8-dioate and carrying out the previously described synthetic sequence for the synthesis of 9a, 400 mg (3% overall yield) of the tetradeuterated bicyclic product 9b was obtained. $\delta^{tms}_{CCl_4}$ 5.64 (singlet, 2H); 2.19 (multiplet, 2H); and 1.19 (multiplet, sharp, 4H). $J_{C^{13}-H}$ to $C^{12}-H$ of the olefinic protons was 11.5 Hz.

Ozonolysis of 9,9-Dichloro-trans-bicyclo [6.1.0] non-cis-4-ene

Approximately 50 mg (0.262 mmole) of 9a were dissolved in 5 ml of absolute methanol, and cooled to -78° in a dry ice-acetone bath. A mixture of 1-2% ozone in oxygen (Welsbach Ozone Generator Model t-408) was bubbled through the solution until the blue color persisted (ca. 15 min.). The excess ozone was then flushed out with oxygen and the methanol solution evaporated at room temperature to a clear colorless syrup. To the syrup were added 3 ml of 90% formic acid and 1.5 ml of 30% H_2O_2. Gentle heat from a flame was then applied until the oxothermic reaction started; this lasted approximately 15 min. The solution was then refluxed for an additional 25 min. and then cooled to -20°. From the solution, 66 mg (97%) of crystals (mp 103-105°) were obtained. This material had identical infrared and nmr spectra to 13g. In addition, a mixture melting point of the two samples gave no depression.

Attempted Addition of p-Methoxyphenyl Azide to 9a

Approximately 250 mg (1.3 mmole) of 9a and 199 mg (1.4 mmole) of p-methoxyphenyl azide were dissolved in 1 ml of ether and placed in the dark under a N_2 atmosphere for 3.0 days at room temperature. At the end of this time tlc and nmr spectroscopy showed no reaction had taken place. The ether was then evaporated to an oil and the oil heated to 60° in an oil bath for 5.5 hours. Again, tlc and nmr spectroscopy showed that no reaction had taken place.

9,9,10,10-Tetrachloro-cis,trans-tricyclo [6.1.0.1^{4,5}] Decane (15) A: From 9a

To 10 ml of pentane (reagent grade) were added 100 mg (0.52 mmole) of 9a and 0.27 mg (5.0 mmole) of sodium methoxide. The mixture was then cooled to 0° in an ice bath, magnetically stirred, and placed in an argon atmosphere. From a dropping funnel was then added, over a period of one hour, 0.5 ml (0.69 g, 3.62 mmoles) of ethyl trichloroacetate. After the addition, the orange mixture was allowed to stir 6 hours additional at 0° and then overnight at room temperature. Water was then added and the mixture shaken and separated. The aqueous layer was then extracted twice with pentane. All pentane extracts were then combined, dried over $MgSO_4$, and evaporated to an oil. Distillation (80-90%/0.2 mm) of this oil gave 131 mg (90%) of a clear oil that crystallized (mp 73-78°). One recrystallization from ethanol gave needles (mp 94-95°). $\delta^{tms}_{CCl_4}$ 1.90-2.60 (multiplet, 4H); and 0.65-1.80 (multiplet, 8H).

Analysis: Calcd. for $C_{10}H_{12}C_4$: C, 43.83; H, 4.41. Found: C, 43.98; H, 4.47.

B: From Authentic cis, trans-1,5-Cyclooctadiene (16)

The reaction of 100 mg (0.92 mmoles) of cis,trans-1,5-cyclooctadiene (16) with 0.54 g (10.0 mmoles) of sodium methoxide and 1.38 g (1.0 ml, 7.24 mmoles) of ethyl trichloroacetate was carried out in the manner described above. Distillation of the crude oily product (80-90°/0.2 mm) gave a clear oil which crystallized in the bulb (mp 84-90°). The infrared and nmr spectra of this material were identical with those of the materials prepared from 9a. In addition, a mixture melting point gave no depression. Yield: 144 mg (59%).

9,9-Dichloro-trans-bicyclo [6.1.0] non-cis-4-ene Oxide

A solution of 121 mg (0.6 mmoles) of 9a in 10 ml of methylene chloride was mixed with 0.24 g of 85% m-chloroperbenzoic acid (corresponds to 1.2 mmoles of the peracid). When solution was complete, the flask was stoppered and cooled to 2-3° for 20 hours. The insoluble material formed was then filtered off and the filtrate washed twice with sat'd. Na_2CO_3, once with water, dried over $MgSO_4$ and evaporated at room temperature to a crystalline residue. Distillation (60-80°/0.15 mm) of the residue afforded 118 mg (90%) of a white solid (mp 68-70°). $\delta^{tms}_{CCl_4}$ 1.95-2.90 (multiplet, 6H); and 0.60-1.70 (multiplet, 6H). Mass spectrum: 207 m/e (M^+).

Analysis: Calcd. for $C_9H_{12}Cl_2O$: C, 52.19; H, 5.84. Found: C, 52.24; H, 5.81.

cis,trans-1,5-Cyclooctadiene (16)

This compound was first prepared from the Di-μ-chlorobis (cis, cis,1,5-cyclooctadiene) dicopper (I) complex using published procedures.[4]

A more convenient preparation consisted of adding 5.0 g (0.046 mole) commercial (cis,cis-1,5-cyclooctadiene followed by 200 ml of reagent grade pentane, 5.0 g of commercial cuprous chloride (0.05 mole) and 300 ml more pentane to a 1.5 l quartz irradiation vessel fitted with a condenser leading to a mercury bubbler. The entire apparatus was flushed with dry nitrogen and irradiated at 2537 Å, using vigorous magnetic stirring, for 24 hours. The solid material was then filtered off and stored in the dark under N_2 at room temperature. Approximately 45 g of this material (the result of 5 runs) was worked up by shaking it with pentane and conc. ammonia until all the solid had dissolved. To the mixture was then added ice and sufficient sodium cyanide to decolorize the solution. The solution was then shaken again and separated. The aqueous layer was then extracted twice more with pentane, and the pentane solutions were combined and dried over $MgSO_4$. Analysis of this solution by gas chromatography (SE-30) showed approximately equal amounts of cis,cis-1,5-cyclooctadiene and cis,trans-1,5-cyclooctadiene along with a small amount of (ca. 1%) trans,trans-1,5-cyclooctadiene. The solution was then concentrated by distillation, using a wire gauze column, to ca. 200 ml. To this solution was added an equal amount of water containing sufficient $AgNO_3$ (usually 10-13 g was required) to eliminate the product peak from a gas chromatogram of the pentane solution. The aqueous layer was then washed once with pentane and to it was added excess conc. ammonia in order to liberate the olefin. The mixture was extracted 3 times with pentane, the pentane solutions combined, dried over $MgSO_4$ and concentrated to about 100 ml by distillation of the pentane through a wire gauze column. Analysis of this solution by gas chromatography showed 99% pure cis, trans-1,5-cyclooctadiene (16) and integration data gave a yield of 8-10 g (30-40%). The product was then stored in solution at -20° until used.

9,9-Dichloro-trans-bicyclo [6.1.0] non-cis-4-ene (9a)

To a solution of 10 g (0.093 mole) of cis,trans-1,5-cyclooctadiene in 100 ml of pentane was added 9.0 g (0.165 mole) of sodium methoxide. A dropping funnel on the flask was then charged with 14.2 g (0.074 mole) of ethyl trichloroacetate. The mixture was then cooled in an ice bath and flushed with argon for 15 minutes after which the ethyl trichloroacetate was added, with magnetic stirring, to the cold mixture for 2 hours. After the addition was complete, the mixture was allowed to stir an additional 2 hours in the ice bath. Workup consisted of adding water to the mixture and 2 extractions with pentane. The pentane solution was then dried over $MgSO_4$ and evaporated to an oil. Distillation of this oil at 60°/0.25 mm afforded 6.1 g (30%) of 9,9-dichloro-trans-bicyclo [6.1.0] non-e-ene 9a. $\delta^{tms}_{CCl_4}$ 5.65 (multiplet, 2H); 2.19 (multiplet, 6H); and 1.21 (broad singlet, 4H).

formation concerning the nature of **1** and **2** was obtained by preparing tetradeuterio analogs **22** and **23** from **9b**. The small amounts of material available precluded separation of **22** and **23**. It was possible, however, to resolve the olefinic peaks in the mixture by high-resolution nmr spectroscopy and to determine $J_{HC=CH}$ from the carbon-13 satellites. These coupling constants are summarized in Table I. It is clear from Table I that, while the values for **9b** and **23** fall within accepted limits for the cis and trans coupling constants, respectively, the coupling constant of **22** is highly unusual for a trans double bond.[8] Since it is known that coupling constants are maximal when C–H single bonds are

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9,9-Dichloro-trans,trans-bicyclo[6.1.0]non-4-ene (1a and 2a)

The mixture of isomers was prepared from 9a by adding 2.0 g (0.0105 mole) of 2a followed by 2.0 g (0.05 mole) of freshly prepared cuprous chloride[23] and 15 ml of pentane to a 60 ml quartz vessel, fitted with a condenser and mercury bubbler. The entire apparatus was flushed with nitrogen and irradiated at 2537 Å for 27.0 hours. Vigorous magnetic stirring prevented material from adhering to the sides of the vessel. Workup consisted of adding the entire mixture to conc. ammonia, decolorizing with sodium cyanide and extracting the mixture 3 times with pentane. The pentane solutions were then dried over $MgSO_4$ and concentrated to ca. 50 ml and extracted with 30 ml of 20% aqueous $AgNO_3$. A gas chromatogram (Fluorosilicone, QF-1) of the pentane solution showed only starting material remained and no evidence of side reactions was seen. The aqueous layer was then washed once with pentane and then treated with excess conc. ammonia and extracted 3 times with pentane. Analysis of these extracts by gas chromatography showed two compounds in a ratio of 5:1.

The pentane extracts were then evaporated at 0° to an oil. Distillation (50°/1.2 mm) of this oil afforded 0.789 g (43%) of the isomer mixture of 1a and 2a. Degassing the reaction mixture prior to irradiation failed to change the yield.

Analysis: Calcd. for $C_9H_{12}Cl_2$: C, 56.56; H, 6.33. Found: C, 56.43; H, 6.25.

This mixture was then separated by preparative gas chromatography on a 20' by 3/8" 10% Fluorosilicone (QF-1) column to give the perpendicular isomer (2a) as the major product, and the parallel isomer (1a) as the minor product.

2a: $\delta^{tms}_{CCl_4}$ 5.35 (multiplet, 2H); 2.40 (multiplet, 6H); 1.25 (broad multiplet, 2H); and 0.5 (multiplet, 2H).

ir: 846; 895 (weak); 1,005; 1,030; 1,080 and 1,170 cm^{-1}.
uv: λ^{hexane}_{max} 1.92 nm.

1a: $\delta^{tms}_{CCl_4}$ 5.50 (multiplet, 2H); 2.48 (multiplet, 6H); 1.65 (multiplet, 2H); and 0.9 (multiplet, 2H).

ir: 820; 937; 1,048; 1,115 and 1,147 cm^{-1}.
uv: λ^{hexane}_{max} 200 nm.

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Ozonolysis of Isomer Mixture (1a and 2a)

A solution of 100 mg (0.52 mmoles) of the 1:5 isomeric mixture of 1a and 2a in 5.0 ml of absolute methanol was cooled in a dry ice-acetone bath and oxygen containing 1-2% ozone (Welsbach Model t-408) was bubbled through the solution until the blue color persisted (ca. 1.0 min.). Oxygen was then bubbled through the solution to remove the excess ozone. The methanol solution was then evaporated at room temperature to a clear colorless syrup. The syrup was then refluxed in 3 ml 90% formic acid and 1.5 ml hydrogen peroxide for 40 minutes. Water was then added to the mixture and the mixture extracted 3 times with ether. The ether was then dried over $MgSO_4$ and evaporated to a pale yellow oil. The oil was then taken up in 10 ml of ether and dried into two 5 ml portions.

Portion A was esterified with diazomethane and a gas chromatogram (SE-30) of the crude product showed that only one substance was present. The retention times correlated well with 13b. Evaporation of the solution to an oil gave 61 mg (85%) of the diester. Comparison of the nmr spectra of this material and 13b confirmed the identity of this material as 13b.

Portion B was evaporated to an oil that slowly crystallized (mp 94-102°) to give 62 mg (93%) of crystalline material. This material gave an identical infrared spectrum to authentic 13g. Crystallization of this material from ether-petroleum ether gave crystals, mp 104-105°. A mixture melting point of this material with 13g gave no depression. In addition, the infrared spectrum of this material was not changed by crystallization.

trans-Bicyclo[6.1.0]non-cis-4-ene[11] (2c)

An ethereal solution of diazomethane was added to a solution of 10 g (0.093 mole) cis,trans-1,5-cyclooctadiene in ca. 50 ml of ether until the yellow color persisted for 30 minutes. The solution was then boiled on the steam bath to remove the excess diazomethane after which it was evaporated to an oil that would not crystallize. The oil was picked up in 500 ml of pentane and irradiated for 12 hours using a 550 w Hanovia medium pressure Hg lamp and Pyrex filter. Distillation of the pentane using a vigreaux column followed by rotary evaporation at 0° gave a yellow oil. Distillation of the oil at 70°/29 mm gave 6.0 g (53%) of trans-bicyclo[6.1.0]non-cis-4-ene (2c).

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trans,trans-Bicyclo[6.1.0]non-4-ene (1b and 2b)

The isomer mixture of 1b and 2b was prepared in a similar fashion to that described earlier for 1a and 2a. To a 60 ml quartz vessel was added 2.0 g (0.0105 mole) of freshly prepared cuprous chloride[23] followed by 1.0 g (8.2 mmoles) of 9c and 10 ml of pentane. After flushing the entire apparatus with nitrogen, the stirred mixture was irradiated at 2537 Å for 28 hours. Workup was accomplished as before using conc. ammonia and sodium cyanide. Analysis of the pentane extracts by gas chromatography (Nitrile Silicone, XF-1150) showed 85% starting material and 20% isomerized products as the only volatile materials present. Separation of the isomerized products was performed as before using 20% aqueous $AgNO_3$. In this case, the product ratio was found by gc to be 1:7. The pentane solution was first distilled using a wire gauze column and then evaporated to an oil. Distillation of the oil at 50°/29 mm afforded the 1b and 2b mixture in 20% yield. Again, degassing the reaction mixture prior to irradiation failed to change the yield.

Analysis: Calcd. for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.18; H, 11.66.

Separation of the two isomers by preparative gas chromatography was achieved using a 12' x 1/2" 20% Nitrile Silicone (XF-1150) column to give 2b as the major product and 1b as the minor product.

2b: $\delta^{tms}_{CCl_4}$ 5.30 (multiplet, 2H); 2.34 (multiplet, 8H); 0.6-1.2 (broad multiplet, 2H); and 0.51 (triplet, 2H).
uv: λ_{max} 197 nm (vacuum).

1b: $\delta^{tms}_{CCl_4}$ 5.52 (unresolved multiplet, 2H); 2.38 (multiplet, 8H); 0.85-1.5 (multiplet, 2H); and 2.27 (quartet, 2H).
uv: λ_{max} 205 nm (vacuum).

9,9-Dichloro-trans,trans bicyclo[6.1.0]non-4-ene Oxide (18)

To a solution of 180 mg (0.95 mmoles) of 2a and 1a (5:1 isomer ratio) in 10 ml of methylene chloride was added 0.35 g (1.72 mmoles) of 85% m-chloroperbenzoic acid. When solution of materials was complete, the flask was stoppered and cooled to 3° for 24 hours. The insoluble material was filtered and the methylene chloride filtrate was washed twice with saturated aqueous Na_2CO_3, once with water and dried over $MgSO_4$. Evaporation at room temperature gave a quantitative yield of crystalline residue. Sublimation of the residue at

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75°/0.2 mm gave a crystalline product, mp 98-104°. A gas chromatogram (Fluorosilicone, QF-1) of the crystalline product showed two products in a 5:1 ratio. After 4 recrystallizations from hexane, the major product (mp 114-116°) was obtained pure (gc) and a crystal submitted for X-ray analysis.

Analysis (mixture): Calcd. for $C_9H_{12}Cl_2O$: C, 52.19; H, 5.84. Found: C, 52.31; H, 5.84.

10,10-Dichloro-trans,trans tricyclo[6.1.0.1^{4,5}]decane (19) from 2a

Granular zinc copper couple was prepared as before.[64] Five grams (1.5 ml, 0.02 mole) of methylene iodide was added, over a period of 15 minutes, to a mixture of 100 mg 2a and 2.0 g (0.08 mole) of couple in 20 ml of anhydrous ether. Once the exothermic reaction was over, the mixture was refluxed for 17 hours. The mixture was then worked up by pouring it into ice and 1N HCl and shaking and separating the ether layer. The ether layer was washed again with 1N HCl, once with water, dried over $MgSO_4$ and evaporated at room temperature to an oil (19) that would not crystallize. A gas chromatogram (SE-30) of this material showed only 85% purity. The oil was finally purified by preparative gas chromatography on a 8' x 1/2" 30% silicone rubber (UC-W) column. $\delta^{tms}_{CCl_4}$ 2.33 (multiplet, 6H); 1.10 (multiplet, 6H); and 0.3 (multiplet, 2H). ir: 780; 805; 908; 1,005; 1,061; 1,220; and 1,445 cm^{-1}.

Analysis: Calcd. for $C_{10}H_{14}Cl_2$: C, 58.55; H, 6.88. Found: C, 58.34; H, 7.01

From 2b

To a solution of 40 mg (0.33 mmoles) of the major isomer of the mixture of 1b and 2b in 7 ml pentane was added 0.4 g (7.4 mmoles) of sodium methoxide. The magnetically stirred reaction mixture was placed under an argon atmosphere and cooled in an ice bath. Over a period of 45 minutes, 0.68 g (3.63 mmoles) of ethyl trichloroacetate was added. The mixture was allowed to stir in the ice bath for 4 hours and then overnight at room temperature. Water was then added followed by 2 extractions with pentane. The pentane solutions were then combined, dried over $MgSO_4$ and evaporated at room temperature to an oil. Distillation of the oil at 60°/0.2 mm gave a clear product that would not crystallize. Analysis by gas chromatography

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(SE-30), however, indicated pure material. Both the nmr and ir spectra of this oil were identical with those of 19 from 2a.

Irradiation of 2a with Cuprous Chloride

The 60 ml quartz tube was charged with 0.27 g (1.41 mmoles) of 2a, 0.3 g (2.9 mmoles) of freshly prepared cuprous chloride[65] and 5.0 ml of pentane. After flushing the entire apparatus with nitrogen, the stirred mixture was irradiated at 2537 Å for 31 hours. Treatment of the entire reaction mixture with conc. ammonia and sodium cyanide was followed by pentane extraction. Analysis of these pentane extracts by gas chromatography (Fluorosilicone, QF-1) showed that 60% of the material had been re-isomerized back to 2a. The remaining 40% was found to be a 5:1 mixture of 2a and 1a, respectively. Only trace quantities of any other volatile materials were detected. A quantitative yield of 9a, 1a and 2a was recovered by distillation (60°/0.2 mm).

Irradiation of 1a and 2a without Cuprous Chloride

To a 3 mm quartz tube was added ca. 10 mg (0.053 mmoles) of 1a and 2a (5:1 ratio of isomers) and 0.5 ml of pentane. The tube was sealed and irradiated at 2537 Å for 22 hours. At the end of this time, a grey amorphous precipitate had formed. Analysis by gas chromatography (Fluorosilicone, QF-1) of the supernatant solution showed only 9a. Both isomers of the starting material had been completely eliminated.

Irradiation of 9a without Cuprous Chloride

A 3 mm quartz tube which contained ca. 10 mg (0.053 mmoles) of 9a and 0.2 ml pentane was first filled with argon and then sealed and irradiated at 2537 Å for 15 hours. At the end of this time, the light yellow solution showed no evidence of polymer formation. Analysis by gas chromatography (Fluorosilicone, QF-1) showed only starting material was present.

Thermal Stability of 9a

The determination was made by adding 40 mg (0.21 mmoles) of 9a, 0.5 ml C_6D_6 and ca. 0.2 mg of hydroquinone to a thick-wall nmr tube. The tube was then filled with argon, sealed, and heated at 250° for 12 hours. Both nmr and gc (Fluorosilicone, QF-1) showed no change had occurred.

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Reaction of 1a and 2a with Sodium Methylsulfinyl Methide

A solution of 183 mg (0.955 mmoles) of 2a and 1a (5:1 mixture of isomers) dissolved in 5.0 ml of pentane was prepared and, at room temperature with magnetic stirring, 3.1 ml (one equivalent) of freshly prepared and filtered 0.3 M sodium methyl sulfinyl methide[62] was added. The mixture turned immediately red-black and moderate heat evolution was noted. The mixture was allowed to stir for 90 minutes after which it was diluted 3-fold with water and extracted 3 times with pentane. The pentane extracts were combined, dried over $MgSO_4$ and evaporated to an ice bath to give 145 mg of residue. To the residue was added 5.0 ml of pentane. Comparison of gc integration data (Fluorosilicone, QF-1) between this solution and the original starting solution indicated only 52 mg (28%) of 1a and 2a remained. No isomerization of 1a and 2a to 9a was detected and attempts to identify the other components of the complex residue failed.

N-Phenyl-10,10-Dichloro-trans,trans-azatricyclo[6.1.0.1^{4,5}]-decane

A solution of 1.5 g (7.9 mmoles) of 2a and 1a (5:1 mixture of isomers) in 10 ml of absolute ether was combined with 0.935 g (7.9 mmoles) of phenyl azide also dissolved in 10 ml of absolute ether. The mixture was then swirled and cooled to 3° for 5 hours. The solvent was evaporated to dryness and then further dried by vacuum (0.05 mm) for 12 hours in the dark. The yield of triazoline adduct was quantitative.

To a Pyrex vacuum sublimation apparatus whose cold-finger condenser was cooled by recirculated ice water was added 2.2 g (7.0 mmoles) of the triazoline adduct and 95 ml of anhydrous acetone (the apparatus was filled sufficiently to give considerable immersion of the cold-finger condenser in the solution). The magnetically stirred solution was then photolyzed using a 275w sun lamp for 12 hours. During the photolysis, the temperature of the solution remained below room temperature at all times. From the photolysis, 157 ml (96% of theory) of nitrogen was collected. The yellow solution was then evaporated to an oil which was picked up in pentane, filtered and cooled to 3°. From the filtrate, 1.6 g (80%) of crystals (mixture of isomers) were collected, mp 115.5-119°.

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Analysis: Calcd. for $C_{15}H_{17}NCl_2$: C, 63.84; H, 6.07 Found: C, 63.65; H, 6.14

Aziridine 21

To a solution of 350 mg (1.83 mmole) of pure 2a in 5 ml of anhydrous ether was added 218 mg (1.83 mmole) of phenyl azide. The resulting solution was cooled in darkness to 3° for 48 hours. Evaporation of the solvent to dryness followed by vacuum drying (0.02 mm) in the dark for 6.0 hours gave the triazoline adduct in quantitative yield.

Photolysis, for 9 hours, of the triazoline in 5 ml anhydrous acetone was carried out as described above.

Evaporation of the acetone solution followed by crystallization of the oil from pentane gave 256 mg (50%) of 21, mp 124-125°. λ^{hexane}_{max} 278 nm (ε 1,820); ir: 700; 768; 797; 929; 1,209; 1,450; 1,499 and 1,610 cm^{-1}. $\delta^{tms}_{CDCl_3}$ 6.70-7.40 (multiplet, 5H); 2.40 (quartet, 4H); 1.87 (doublet, 2H) and 0.85-1.60 (multiplet, 6H). Mass Spectrum: 282 m/e (M^+).

Aziridine 20

Preparation of this material from 100 mg (0.525 mmole) of pure 1a and 62 mg (0.525 mmole) of phenyl azide was carried out in the

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same manner as described earlier for 21. Subsequent photolysis yielded material which could be crystallized from pentane, 37 mg (27%), mp 72.5-73.5°. λ^{hexane}_{max} 278 nm (ε 1,800); ir: 700; 770; 805 (broad); 929; 945; 1,209; 1,320; 1,499 and 1,610 cm^{-1}. $\delta^{tms}_{CDCl_3}$ 6.70-7.40 (multiplet, 5H); 2.41 (doublet, 4H); 2.09 (doublet, 2H) and 0.85-1.65 (multiplet, 6H). Mass Spectrum: 282 m/e (M^+). The cracking pattern was identical to that obtained for 20. This material is quite difficult to crystallize.

Thermal Chemistry of 2b

The procedure was carried out by dissolving ca. 100 mg (0.82 mmoles) of 2b in 1 ml of hexane (which had been shaken with conc. H_2SO_4) and sealing in a 6 mm Pyrex glass tube. The tube and contents were heated at 138° over a stream of refluxing xylene for 84 hours. At the end of this time, gc analysis (silicone nitrile, XF-1150) indicated that no change had occurred in the mixture.

Thermal Chemistry of 1b

The procedure was carried out using ca. 100 mg (0.82 mmoles) of 1b and 1 ml of hexane in a similar manner to the pyrolysis of 2b. At the end of 24 hours, gc analysis (silicone nitrile, XF-1150) showed 12% conversion to 9b. After another 58 hours of heating, 31% of the material had been isomerized to 9b. No other

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reaction products were found.

Pyrolysis of 1b and 2b in the Presence of Base

To ca. 100 mg of 1b and 2b (the 7:1 mixture of isomers) was added 1 ml of hexane and 0.5 ml of quinoline. The mixture was then sealed in a 6 mm Pyrex tube and heated at 138° for 35 hours using a stream of refluxing xylene. At the end of this time, a considerable amount of 9b had been formed.

Pyrolysis of Aziridine 21

The reaction was carried out by dissolving 50 mg (0.177 mmoles) of 21 in 1 ml of hexane and sealing the mixture in a 6 mm Pyrex tube. The tube and contents were then heated to 138° over a stream of refluxing xylene for 67.0 hours. When the tube had cooled, a crystalline substance appeared (mp 123-124°) and appeared from tlc (50:50 C_6H_6 petroleum ether) to be unreacted starting material.

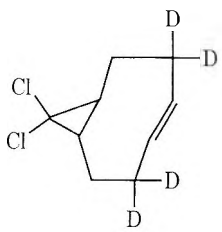
Pyrolysis of 20

This reaction was carried out using ca. 15 mg 20 (0.053 mmoles) and 1 ml of hexane sealed in a 6 mm Pyrex tube. The tube was heated to 138° as before for 60 hours. Upon cooling of the tube, no crystals formed, but tlc (50:50 C_6H_6-petroleum ether) indicated that no change had occurred.

Table I
Olefinic Vicinal Coupling Constants of the Tetradeuterated Trans-Fused Bicyclo[6.1.0]non-4-ene Isomers

Compound	$J_{H-C^{13}=C^{12}-H}$, Hz
9b (cis)	11.5
22 (trans-parallel)	11.0
23 (trans-perpendicular)	16.5

coplanar, we believe that the reduced coupling constant for **22** indicates the presence of noncoplanar olefinic C–H bonds.



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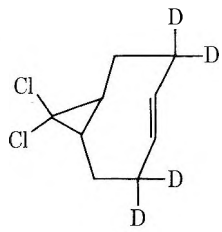

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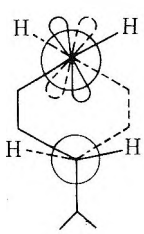
Two possible conformations for nonplanar strained double bonds have been proposed, discussed, and experimentally observed in the literature. The first of these, exemplified by structure **24**, retains the sp^2 hybridization and results in a skewing of the substituents.[16a-c] The second of these, **25**, involves the rehybridization of the two olefinic



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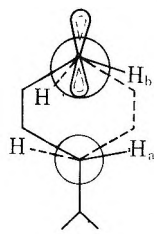

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carbons and retains the eclipsed arrangement of the substituents.[16c-e] Formation of either structure **24** or **25** would effectively move the π bond further away from the cyclopropane ring and thereby diminish interaction between the π bond and the internal cyclopropane ring bond. Since such repulsions are almost certainly greater in the case of the parallel form, it is not surprising that the parallel isomers show a much greater tendency to relieve such interactions. Although the π–σ interactions may be smaller in structure **25**, it appears that transannular H_aH_b interactions are much less severe in **24**. Unfortunately, the available data do not allow a distinction between **24** and **25**. It is also impossible to relate quantitatively the magnitude of the deviation to the observed coupling constants.

Structures **1** and **2** are much more stable than their diene analogs **6** or **7**. They were indefinitely stable when kept at −20° in a dilute hexane solution and reasonably stable in solution at room temperature under nitrogen. It was hoped that the forced close proximity of the π bond and the cyclopropane might force forbidden 2 + 2 cycloadditions. Instead, at elevated temperatures, the parallel isomer **1b** was slowly converted to the cis,trans isomer **9c**. For example, when **1b** was heated at 138° for 84 hr, glc analysis indicated 31% conversion to **9c**. The extent of isomerization was not effected by the presence of quinoline which indicates that the isomerization is not acid catalyzed. By contrast, **2b** and **9c** were unchanged when heated at this temperature for the same period of time.[17] The facility of this unprecedented thermal isomerization of an isolated double bond lends

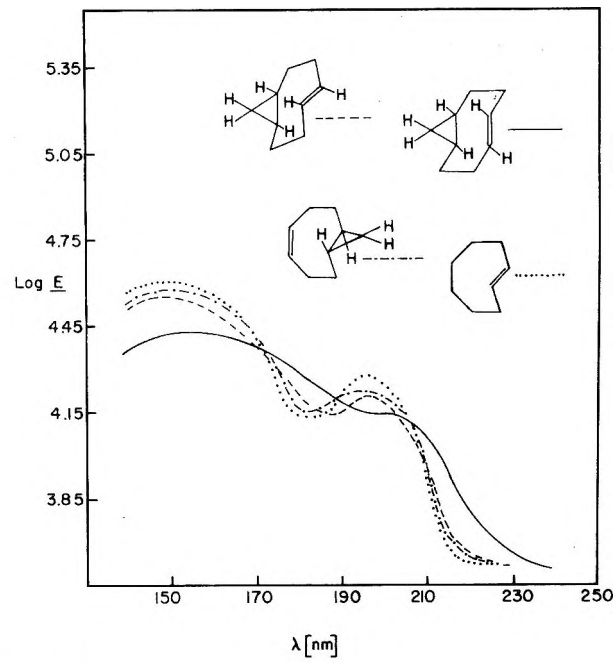
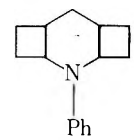


Figure 1.

chemical support to the postulated weakened, distorted π bond depicted in **24** (or possibly **25**).

The photochemistry of **1** and **2** was also briefly investigated for signs of internal cycloaddition. The irradiation at 2537 Å of a mixture of **1a** and **2a** in hexane for 22 hr resulted in conversion to the cis,trans isomer **9a** along with the formation of considerable gray polymer. No starting material or other volatile products were formed. Similar treatment of **9a** resulted in neither change nor polymer. A final attempt at cycloaddition in this system with aziridines **21** and **20** was made. It is known that aziridines undergo thermal conrotatory ring opening to azomethine ylides. Although such intermediates might have added across the cyclopropane ring bond to give products such as **26** and



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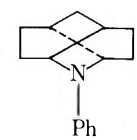

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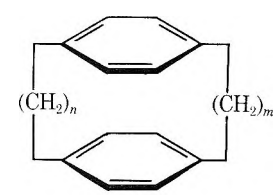
27, both **20** and **21** were recovered unchanged when heated at 138° for 60 hr.

In order to further assess the nature of the transannular interaction, vacuum ultraviolet spectra were obtained for **1b**, **2b**, and **9c**. These spectra are reproduced in Figure 1 along with, for purposes of comparison, *trans*-cyclooctene. From these spectra it can be seen that the parallel form **1b** has the longest wavelength maximum and that both the σ–σ^* and π–π^* absorption bands are considerably broadened for the parallel form. The shift to longer wavelengths appears to be indicative of transannular resonance stabilization in the excited state. A similar observation has been made by Cram in the paracyclophane series (**28**) where m and n are small (*e.g.*, when $m = n = 2$).[19] It is interesting



28

to note that shifts to longer wavelengths in the paracyclophane series were also associated with broadened bands and decreased absorption intensities.

The properties of **1** are thus vastly different from the perpendicular isomer **2** or other analogous *trans*-alkenes. The difference appears attributable to the transannular repulsions between the π bond and the cyclopropane ring. These repulsions distort the π bond and thus greatly alter its chemical reactivity. Further studies on these and related distorted alkenes should clarify the precise nature of the distortion process and the chemical consequences of such distortions. Finally, it is apparent that the unique features of the trans,trans arrangement present in these compounds offer many opportunities for chemical study of previously unavailable molecular arrangements.[20]

Registry No.—**1a,** 36217-82-0; **1b,** 36217-84-2; **2a,** 36217-81-9; **2b,** 36217-83-1; **6,** 1552-12-1; **9a,** 36217-85-3; **9a** oxide, 53447-31-7; **9b,** 53447-32-8; **9c,** 36217-86-4; **13b,** 53384-96-6; **13c,** 53432-89-6; **13d,** 53384-97-7; **13e,** 53384-98-8; **13f** (X = I), 53384-99-9; **13f** (X = Cl), 53385-02-7; **13g,** 36217-87-5; **15,** 53447-33-9; **16,** 5259-71-2; 18, 36217-88-6; **19,** 53447-34-0; **20,** 53385-00-5; **21,** 53447-36-2; **22,** 53447-35-1; **23,** 53447-37-3; phenyl azide, 622-37-7; sodium methylsulfinyl methide, 15590-23-5; cuprous chloride, 7758-89-6; *p*-methoxyphenyl azide, 2101-87-3; di-*tert*-butyl *trans*-4-octene-1,8-dioate, 53432-90-9; di-*tert*-butyl 2,2,7,7-tetradeuterio-*trans*-4-octene-1,8-dioate, 53385-01-6; triphenylphosphine, 603-35-0; sodium iodide, 7681-82-5; *p*-toluenesulfonyl chloride, 98-59-9; dimethyl *trans*-4-octene-1,8-dioate, 32456-97-6; sodium trichloroacetate, 650-51-1.

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Synthesis of Some *cis*- and *trans*-2-Dimethylaminomethyl Cyclic Amines and Related Diamines[1]

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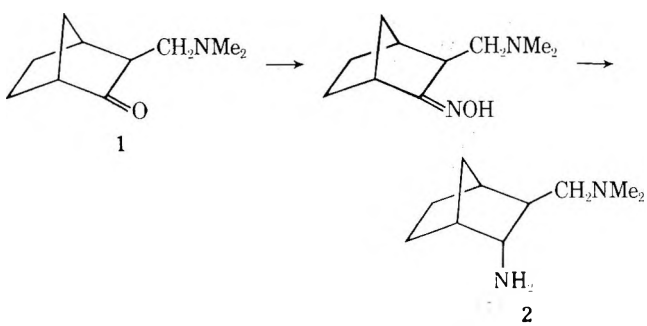
The preparation of *N,N*,2,2-tetramethyl-1,3-propanediamine, *cis*- and *trans*-2-(dimethylaminomethyl)cyclohexylamine, and 3-*exo*-dimethylaminomethyl-2-*endo*-norbornanamine has been accomplished by the Mannich reaction on the appropriate carbonyl compound, followed by oximation and reduction. The reactions of methacrolein and 3-methylene-2-norbornanone with methylhydrazine gave pyrazolines whose methiodides were reduced to *N,N*,2-trimethyl-1,3-propanediamine and 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine, respectively.

The dedeuteration of acetone-d_6 has been shown to be catalyzed bifunctionally by the monoprotonated form of *N,N*-dimethyl-1,3-propanediamine.[2,3] Examination of models of the transition state of the rate-controlling step in the reaction showed that in the two most stable conformers the carbon-1–nitrogen bond from the diamine was approximately eclipsed with a carbon-2–hydrogen or carbon-2–carbon-3 bond. The greatly increased bifunctional catalytic activity of both the cis and trans isomers of 2-(dimethylaminomethyl)cyclopentylamine experimentally demonstrated the importance of conformational effects.[2,3] To study such effects in more detail we have synthesized several additional conformationally constrained derivatives of *N,N*-dimethyl-1,3-propanediamine and also two 1,4-diamines.

Results

The method used previously for the preparation of the 2-(dimethylaminomethyl)cyclopentylamines, in which the Mannich reaction is used to introduce a dimethylaminomethyl substituent into a carbonyl compound that is then transformed to its oxime and reduced,[3] was used to prepare *N,N*,2,2-tetramethyl-1,3-propanediamine and the 2-(dimethylaminomethyl)cyclohexylamines, which were obtained as a mixture containing about 60% of the major and 40% of the minor isomer. After separation by fractional crystallization of the oxalate salts, the major product was assigned the cis and the minor one the trans configuration on the basis of their pmr spectra. The carbon-1 proton of the cis isomer, which should be largely equatorial, absorbed at about 0.5 ppm lower field than the carbon-1 proton of the trans isomer, which should be largely axial.[4a] In the presence of the shift reagent Eu(fod)$_3$[5] the widths at half-height for the carbon-1 proton peaks were *ca.* 12 and *ca.* 30 Hz for the cis and trans isomers, respectively. The peak for the largely axial carbon-1 proton of the trans isomer is broadened by two large axial–axial vicinal coupling constants, whereas the peak for the largely equatorial carbon-1 proton of the cis isomer is much less extensively split.

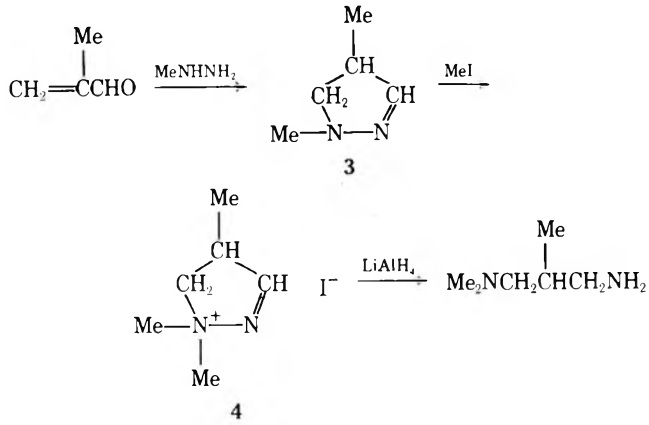
Application of the same method of synthesis to 2-norbornanone as the starting material gave, as the product of the first step, the 3-(dimethylaminomethyl)-2-norbornanone (**1**) that has been shown by Krieger to be exo.[6] This stereochemical assignment is supported by pmr measurements using a shift reagent. Oximation of the ketone and lithium aluminum hydride reduction gave 3-*exo*-dimethylaminomethyl-2-*endo*-norbornanamine (**2**). The pmr peak for

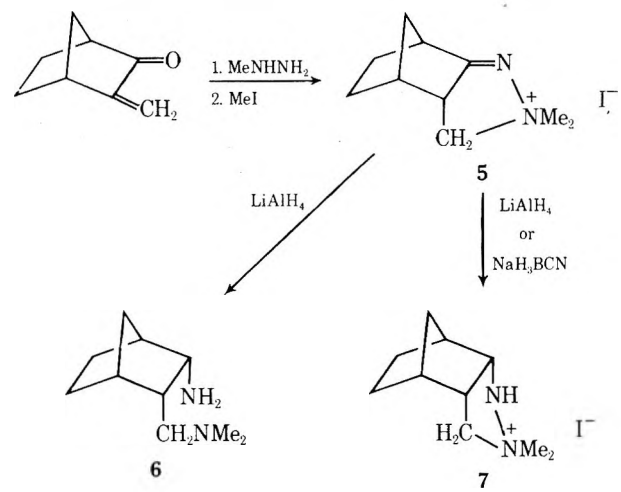


the carbon-2 proton was split with coupling constants of about 1, 4.5, and 4.5 Hz. The latter two coupling constants are plausible for vicinal exo–bridgehead coupling and exo–endo coupling.[4b,7] The coupling constant of *ca.* 1 Hz probably arises from long-range splitting by the exo proton on carbon-6. If the new primary amino group had been exo the carbon-2 proton peak would have been split by the carbon-3 proton with a coupling constant of about 7 Hz and by no other coupling constant larger than 3 Hz.[4b,7]

Since the synthesis of **2** gave no clearly observable amount of a cis isomer, we devised a stereospecific synthesis to obtain such a compound. The required groups would be held cis by being in a five-membered ring, whose cleavage would be the last step of the reaction. The preparation of *N,N*,2-trimethyl-1,3-propanediamine was used as a proving ground for this new stereospecific synthesis. By analogy to the reaction of α-methylene ketones with methylhydrazine to give pyrazolines,[8,9] methacrolein was transformed to 1,4-dimethyl-2-pyrazoline (**3**), which was methylated with methyl iodide at its saturated nitrogen atom.[10] Lithium aluminum hydride reduction of the resulting pyrazolinium salt **4** gave the desired diamine in 19% yield (not optimized).

When this method of synthesis was applied to 3-methylene-2-norbornanone, lithium aluminum hydride reduction of the pyrazolinium salt **5** gave 15% 3-*endo*-dimethylaminomethyl-2-*endo*-norbornanamine (**6**) and 22% of the product **7** in which only the double bond had been reduced.

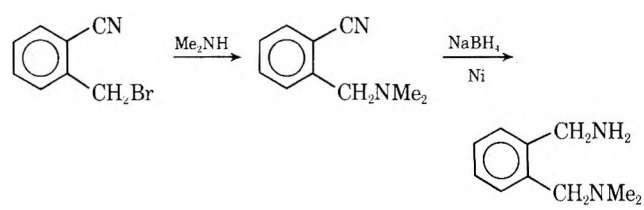




The latter was the only product obtained (in 46% yield) when **5** was reduced with sodium cyanoborohydride in methanol at about pH 4. The C-2 proton peak for **6** was a doublet of doublets (J = 9.5, 4.5 Hz). The larger of these coupling constants shows that **6** must be a cis isomer and very probably an endo cis isomer.[4b,7] The smaller coupling constant, which is too large for any possible long-range coupling or for bridgehead–endo vicinal coupling in the norbornane series, is perfectly plausible for bridgehead–exo vicinal coupling.

We believe that the pyrazoline route we have used may prove to be a rather general method for the stereospecific synthesis of derivatives of *cis*-(2-aminomethyl) cyclic amines.

Also prepared was o-(dimethylaminomethyl)benzylamine, which was synthesized from *o*-cyanobenzyl bromide by reaction with dimethylamine followed by sodium borohydride–Raney nickel reduction.[11]



Reductive methylation of the appropriate primary-tertiary diamines was used to prepare o-bis(dimethylaminomethyl)benzene, which has been made in other ways,[12,13] and *N,N,N′,N′*,2,2-hexamethyl-1,3-propanediamine.

Experimental Section[14]

2,2-Dimethyl-1-dimethylaminopropylamine.--A concentrated aqueous solution of 14.1 g of sodium carbonate was added dropwise to a cold mixture of 34.3 g of 2,2-dimethyl-3-dimethylaminopropanal and a saturated aqueous solution of 20.3 g of hydroxylamine hydrochloride. After about 1 hr of stirring 18.9 g (49%) of the oxime was obtained as white crystals: mp 51--55°; ir (KBr) 3050, 3150 (s, O-H), 1630 (w, C=N), 954 (s, N-O), 1470 (m), 1450 (m), 1420 (m), 1350 (w), 1300 (m), 1230 (w), 1165 (m), 1105 (w), 1040 (m), 1026 (s), 998 (w), 927 (s), 870 (m), 775 (m), 635 (w), 508 cm^{-1} (w); pmr ($CDCl_3$) δ 1.10 (s, 6, CH_3C), 2.28 (s, CH_3N) and 2.30 (s, CH_3)--8.2 protons, and 7.37 ppm (s, 1, CH=N).

After slow addition of 9 g (0.063 mol) of oxime to 4.94 g (0.130 mol) of lithium aluminum hydride in 250 ml of ether with stirring, the solution was refluxed for 48 hr. Addition of 10% aqueous sodium hydroxide gave a white precipitate that was removed by filtration. Distillation of the filtrate gave 4.71 g (58%) of 2,2-dimethyl-3-dimethylaminopropylamine: bp 152.5--153°; ir (neat) 3370 and 3280 (w, NH_2), 2940, 2860, 2810, and 2760 (all s, C-H), 1590 (w), 1450 (m), 1340 (w), 1370 (w), 1240 (w), 1155 (w), 1100 (w), 1050 (s), and 850 cm^{-1} (m); pmr ($CDCl_3$) δ 0.83 (s, 6, CH_3C), 1.13 (s, 2, NH_2), 2.05 (s, 2, CH_2NMe_2), 2.20 (s, 6, CH_3N), and 2.43 ppm (s, 2, CH_2NH_2); exact mass of parent ion, calcd 130.14698, found 130.14715.

2-(Dimethylaminomethyl)cyclohexylamines.--The oxime of 2-(dimethylaminomethyl)cyclohexanone has been reduced catalytically[15] and with sodium in liquid ammonia,[15] but the products were not separated into cis and trans isomers nor was their stereochemistry studied. A solution of 8.67 g (0.051 mol) of this oxime was refluxed with 7.6 g (0.20 mol) of lithium aluminum hydride in 500 ml of ether. After the usual work-up vacuum distillation gave 6.0 g (76%) of liquid: bp 39--42° (0.11 mm); ir (neat) 3285 and 3360 cm^{-1} (NH_2). Glpc of this liquid on a 12-ft column containing 20% mannitol and 5% potassium hydroxide on Chromosorb-P at 155° showed two overlapping peaks, of which the first was 50% larger than the second. When the oxalate salts were crystallized from 9:1 methanol--water the salt of the major isomer crystallized first. Repeated crystallization of the remaining salt mixture from ethanol gave the pure salt of the minor isomer. The amines were liberated from their oxalates with potassium hydroxide. The major isomer is taken to be cis-2-(dimethylaminomethyl)cyclohexylamine: pmr ($CDCl_3$) δ 2.12 (s, 6, CH_3N), 3.00 (multiplet about 12 cps wide at half-height, 1, H-1), 1.0--2.1 ppm (m, ~13); exact mass of parent ion, calcd 156.16264, found 156.16278. The minor isomer was taken to be trans-2- (dimethylaminomethyl)cyclohexylamine: pmr ($CDCl_3$) δ 2.12 (s, 6, CH_3N), 2.0--2.6 (m, ~3, H-1 and CH_2N), 0.9--2.0 ppm (m, ~11); in the presence of Eu(fod)$_3$ the H-1 peak had a width at half-height of 30 cps.

Anal. Calcd for $C_8H_{18}N_2$: C, 69.17; H, 12.90; N, 17.93. Found: C, 68.83; H, 13.03; N, 17.81.

3-exo-Dimethylaminomethyl-2-norbornanone.--This compound was made from 2-norbornanone by the Mannich reaction.[6] Although the pmr spectra in chloroform-*d* and benzene-d_6 were consistent with the structure assigned previously,[6] they added no evidence for it. However, in the presence of enough (less than 0.1 mol per mol of compound) Eu(fod)$_3$ to shift the 6-proton peak for the dimethylamino group to δ 6.90 there was a 1-proton broadened doublet (J = 12 cps) of doublets (J = 7 cps) at δ 5.99, a 1-proton broadened triplet (J~7 cps) at δ 4.57, a 1-proton broad (8 cps at half-height) singlet at δ 3.51, and a 1-proton doublet (J = 12.5 cps) of doublets (J = 8 cps) at δ 2.82, in addition to the large multiplet stretching from δ 1.0 to 2.5 ppm. Since the coupling constant of 12.5 cps is plausible only for geminal coupling in the present case, and since the peak due to at least one of the two nonequivalent hydrogen atoms of the methylene part of the dimethylaminomethyl group should be shifted about as much as that for the dimethylamino hydrogen atoms, the peaks at δ 5.99 and 2.82 ppm must arise from these two hydrogen atoms. They split the peak for the vicinal hydrogen atom on carbon-3 of the ring system into the apparent triplet seen at δ 4.57 ppm. If this hydrogen atom were exo its peak should also be split by the vicinal bridgehead hydrogen atom with a coupling constant of 3--4 cps.[4b] No additional splitting of this magnitude could be seen in our spectrum, which is consistent with a coupling constant in the range 0--2 cps to be expected for vicinal splitting between a bridgehead hydrogen atom and an endo hydrogen atom.[4b]

Reaction of 34.0 g (0.200 mol) of 3-exo-dimethylaminomethyl-2-norbornanone with 14 g (0.20 mol) of hydroxylamine hydrochloride overnight at room temperature, followed by treatment with 8 g (0.20 mol) of sodium hydroxide gave 30 g (82%) of a white powder; mp (after recrystallization from methanol) 188--191°; ir (KBr) 3050, 3175 (s, OH), 2945, 2910, 2850, 2820, 2775 (all s, CH), 1650 (w, C=N), 1430 (s, CH_2), 1279, 1250 (w), 1165 (m), 1100, 1042 (w), 1012 (m), 933 (s, NO), 912, and 820 cm^{-1} (m); pmr ($CDCl_3$) showed peaks at δ 2.25 and 2.35, attributed to the dimethylamino protons of syn and anti isomers, and other absorption from 1.0 to 3.6 ppm (the solution being dilute because of the low solubility of the oxime); exact mass of parent ion, calcd 182.14189, found 182.14223.

Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 65.89; H, 9.96; N, 15.12.

3-exo-Dimethylaminomethyl-2-endo-norbornanamine.--A solution of 7.1 g (0.039 mol) of the oxime of 3-exo-dimethylaminomethyl-2-norbornanone[6] was refluxed with 6.0 g (0.15 mol) of lithium aluminum hydride in 700 ml of ether under nitrogen for 44 hr. After the usual work-up, vacuum distillation gave 5.0 g (76%) of colorless liquid, bp 49° (0.12 mm), whose glpc showed traces of several impurities. Recrystallizations of the oxalate salt from methanol--ethanol and liberation of the free amine with potassium hydroxide gave pure 3-exo-dimethylaminomethyl-2-endo-norbornanamine: ir (neat) 3290, 3365 (m, NH_2), 2950, 2870, 2820, 2770 (s, CH), 1570 (m), 1450 (s, CH_2), 1365 (m, CH_3), 1260 (m), 1180, 1156 (w), 1043 (s), and 837 cm^{-1} (m); pmr ($CDCl_3$) δ 2.67 (broadened triplet, 1, J~4.5, 1 cps, $CHNH_2$) 2.12 (s, ~6, CH_3N), 1.75--2.17 (m, ~4, $CHCH_2N$ and N-1), 0.67--1.67 ppm (m, ~9); exact mass of parent ion, calcd 168.16264, found 168.16288. Amine hydrochloride, mp 309--311 (d) from EtOH--MeOH (1:1).

Anal. of the hydrochloride. Calcd for $C_{10}H_{22}N_2Cl_2$: C, 49.80; H, 9.19; N, 11.61. Found: C, 49.75; H, 9.14; N, 11.53.

1,1,4-Trimethyl-2-pyrazolinium Iodide.--The method of Ioffe and Zelenin[17] was used to prepare 1,4-dimethyl-2-pyrazoline: ir (neat) 3050 (w, sp^2-CH), 2750--3000 (s, sp^3-CH), 1630 (w, C=N), 1560 (w), 1430 (m), 1360 (w, CH_3), 1298, 1279 (w), 1220, 1200, 1165, 1128 (m), 1080, 1065, 1045 (w), 963, 940 (m), 886, 859, 832, 810, 775 (m), 739, 655, and 608 cm^{-1} (w); pmr ($CDCl_3$) 1.13 (d, 3, J = 6.2 cps, CH_3C), 2.42 (m, 1, N=C-CH), 2.77 (s, 3, CH_3N), 2.83--3.37 (m, 2, CH_2N), and 6.58 ppm (broad s, 1, N=CH). After 30.5 g (0.31 mol) of this pyrazoline and 59.6 g (0.42 mol) of methyl iodide in 150 ml of benzene had stood overnight at room temperature, 67.5 g (90%) of crude yellow 1,1,4-trimethyl-2-pyrazolinium iodide had separated. Two recrystallizations from methanol gave pure light yellow crystals: mp 142--145°, ir (KBr) 2975, 2875 (s, CH), 1610 (w, C=N), 1280, 1260, 1230 (m), 1112, 1058, 990 (w), 930 (s), 875 (w), 825, 765, and 705 cm^{-1} (m); pmr (D_2O)[18] δ 1.38 (d, 3, J = 6.5 cps, CH_3C), 3.37 (s, one CH_3N), 3.52 (s, the other CH_3N), 3.33--4.50 (m, CH_2CH), and 8.13 ppm (broad s, 1, N=CH).

2-Methyl-1-dimethylaminopropylamine.--A suspension of 33 g (0.137 mol) of 1,1,4-trimethyl-2-pyrazolinium iodide and 7.9 g (0.2 mol) of lithium aluminum hydride in 400 ml of ether was refluxed for two days and worked up in the usual manner. Distillation gave 2.97 g (19%) of 2-methyl-3-dimethylaminopropylamine: bp 141--142° (lit.[19] 145--150°); ir (neat) 3275 and 3350 cm^{-1} (NH_2); pmr ($CDCl_3$) δ 0.89 (d, 3, CH_3C), 1.32 (s, 2, NH_2), 1.63 [m, 1, $CH(C)_2$], 2.11 (m, 2, CH_2NMe_2), 2.17 (s, 6, CH_3N), and 2.62 ppm (m, 2, CH_2NH_2); exact mass of parent ion, calcd 116.13137, found 116.13148.

Anal. Calcd for $C_6H_{16}N_2$: C, 62.01; H, 13.88; N, 24.11. Found: C, 61.38; H, 13.78; N, 24.09.

4-Methyl-3,4-diazatricyclo[5.2.1.0^{2,6}]-2-decene.--A solution of 20 g (0.164 mol) of 3-methylene-2-norbornanone[6] in 100 ml of methanol was added dropwise to 14.8 g (0.32 mol) of methylhydrazine in 80 ml of methanol and refluxed for 3 hr. The solvent and excess methylhydrazine were removed at reduced pressure and the residue vacuum distilled to give 20.1 g (82%) of clear yellow liquid product; bp 56--58° (0.21--0.22 mm); ir (neat) no NH absorption, 2955 (s), 2875 (m), 2830, 2730 (w), 1630 (w, C=N), 1430 (m), 1250, 1226, 1191, 1160 (w), 1137, 1123 (m), 1102, 953, 932 (w), 905 (m), 869, 832 (w), 807 (s), and 759 cm^{-1} (w); pmr ($CDCl_3$) δ 2.72 (s, 3, CH_3) and absorption from 11 other protons spread from 1.17 to 2.67 ppm; uv max (*n*-hexane) 255 nm, (95% ethanol) 246 nm. This hypsochromic shift is in the range of those observed with some other pyrazolines on going from *n*-heptane to ethanol and water.[20]

The methiodide (5) was made from 3.47 g (0.023 mol) of this pyrazoline in 5 ml of benzene by adding 2 ml of methyl iodide in 10 ml of benzene dropwise with cooling. After several hours at room temperature filtration and recrystallization from methanol gave 4.34 g (65%) of methiodide; mp 175--178°; ir (KBr) 2940, 2870 (s, CH), 1620 (m, C=N), 1420 (m, CH_2), 1290, 1265 (m), 1235, 1120 (w), 1098 (m), 1057, 1010, 992, 955, 945 (w), 870 (m), 800, 763 (w), and 636 cm^{-1} (m); pmr (D_2O)[18] δ 3.31 (s, 3, one CH_3N), 3.48 (s, 3, the other CH_3N), 3.58--4.33 (m, 2, CH_2N), and broad absorption from 1.0 to 3.33 ppm.

3-endo-Dimethylaminomethyl-2-endo-norbornanamine.--Gradual addition of 36 g (0.123 mol) of the methiodide 5 to 9.5 g (0.25 mol) of lithium aluminum hydride in 600 ml of ether was followed by 56 hr of refluxing under nitrogen. After addition of 10 ml of water, 10 ml of 15% aqueous sodium hydroxide, and 30 ml of water with agitation, the ether layer was separated and the residue extracted with ether. Concentration and vacuum distillation of the ether solutions gave 3.5 g of material whose glpc showed it to be about 90% pure. Glpc purification on a 12-ft, 20% mannitol, 5% potassium hydroxide, Chromosorb P column gave pure 3-endo-dimethylaminomethyl-2-endo-norbornanamine: ir (neat) 3300, 3370 (w, NH_2), 2945 (s), 2865, 2850, 2810, 2760 (m, CH), 1590 (w), 1450 (m, CH_2), 1370, 1350 (w), 1290, 1262, 1190, 1162, 1105, 1050 (w), 1022 (m), and 855 cm^{-1} (m); pmr ($CDCl_3$) δ 3.33 (d of d, 1, J = 9.5, 4.5 cps, $CHNH_2$), 2.18 (s, 6, CH_3N), and 1.1--2.9 ppm (m, 13); exact mass of the parent ion, calcd 168.16264, found 168.16283.

The ether-insoluble material from the lithium aluminum hydride reduction was extracted with warm methanol. After several recrystallizations from 1:1 methanol--ethanol these extracts yielded 7.6 g (22%) of 7 as white needles: mp 192--193°; ir (KBr) 3425 (m, NH), 3150 (s), 2999, 2960, 2900, 2870 (s, CH), 1700 (w), 1450 (s, CH_2), 1425, 1380, 1340, 1300, 1292, 1252 (m), 1237, 1215, 1194, 1168 (w), 1124 (m), 1087, 1152 (w), 1020 (s), 989, 963, 958 (m), 933 (w), 921, 917 (m), 885 (w), 860 (m), 842, 817, 799 (w), 772 (m), 735 (m), 635 (m), 582, 529, and 457 cm^{-1} (w); pmr (D_2O)[18] δ 4.02 (d of d, J = 10.5, 5 cps, one CH_2N proton), 3.63 (d of d, J = 10.5, 2 cps, the other CH_2N proton), 3.42 (s, one CH_3N), 3.34 (s, the other CH_3N), and broad absorption from 1.33 to 3.50 ppm.

Anal. Calcd for $C_{10}H_{19}N_2I$: C, 40.83; H, 6.51; N, 9.52. Found: C, 40.63; H, 6.63; N, 9.25.

A solution of 4.34 g (0.015 mol) of 5 and 1.7 g (0.027 mol) of sodium cyanoborohydride in 100 ml of methanol at about pH 4.4 was stirred for 4.5 hr at room temperature, then concentrated, added to water, and made basic with 1 M sodium hydroxide. Several extractions with ether, concentration, and recrystallizations from ethanol--methanol gave 2 g (46%) of 7, ir and pmr identical to that obtained as described in the preceding paragraph.

o-(Dimethylaminomethyl)benzonitrile.--Dropwise addition of 40 g (0.204 mol) of *o*-cyanobenzyl bromide in 150 ml of benzene to about 100 g of cold dimethylamine was followed by 3 hr of stirring at room temperature. After removal of a white precipitate by filtration the solution was concentrated and vacuum distilled to give 25.5 g (78%) of *o*-(dimethylaminomethyl)benzonitrile: bp 62--63° (0.14 mm); ir (neat) 2230 (s, C≡N), 1600 (w, aromatic C=C), 3030 and 3070 (w, aromatic C-H), 2980 (m), 2950 (m), 2860 (m), 2825 (m), 2775 (m), 1480 (w), 1450 (m), 1355 (m), 1250 (m), 1160 (m), 1155 (w), 1100 (w), 1035 (s), 850 (w), 857 (w), 770 (s), and 718 (w); pmr ($CDCl_3$) δ 2.29 (s, 6, CH_3N), 3.64 (s, 2, CH_2), and 7.2--7.8 ppm (m, 4, aromatic CH); exact mass of parent ion, calcd 160.10004, found 160.10027.

o-(Dimethylaminomethyl)benzylamine.--A solution of 3.15 g of sodium borohydride in 12 ml of 8 M aqueous sodium hydroxide was added dropwise to 13.3 g (0.083 mol) of *o*-(dimethylaminomethyl)benzonitrile and 5 g of Raney nickel in 40 ml of methanol. After the evolution of hydrogen had stopped the solution was filtered, concentrated, and about half of it accidentally spilled. Treatment of the remainder with 9 g of potassium hydroxide caused the separation of about 5 g of an oil that was distilled to give 4 ml of *o*-(dimethylaminomethyl)benzylamine: bp 61.5--62° (0.2 mm); ir (neat) 3260, 3350 (w, NH_2), 3060, 3010 (w, sp^2-CH), 2975, 2940, 2855, 2810, 2760 (m, sp^3-CH), 1590 (w), 1450 (m), 1350 (m), 1255, 1178 (m), 1100 (w), 1050 (m), 1025 (s), 850, 755, and 740 cm^{-1} (m); pmr ($CDCl_3$) δ 1.81 (s, 2, NH_2), 2.20 (s, 6, CH_3N), 3.43 (s, 2, CH_2), 3.84 (s, 2, CH_2), and 7.13--7.38 ppm (m, 4, aromatic CH).

Anal. of the hydrochloride. Calcd for $C_{10}H_{16}N_2Cl_2$: C, 50.64; H, 7.65; N, 11.81. Found: C, 50.03; H, 7.64; N, 11.53.

In another run in which poor quality sodium borohydride was used the product obtained contained 18% starting material, but the yield was 65% (corrected for the impurity).

N,N,N',N',2,2-Hexamethyl-1,3-propanediamine.--To 9.6 ml (0.25 mol) of ~98% formic acid was added 4.64 g (0.0357 mol) of N,N,2,2-tetramethyl-1,3-propanediamine slowly with cooling and stirring. After 11 ml (0.14 mol) of 37% formaldehyde had been added the solution was refluxed for 15 hr, cooled, acidified with 36 ml of 4 N hydrochloric acid, and evaporated to dryness. Solution of the residue in 20 ml of water and treatment with 20 ml of 18 N sodium hydroxide caused an oil to separate. The oil was combined with two 15-ml benzene extracts of the aqueous layer, dried over potassium carbonate, and distilled through a 13-cm Vigreux column to give 3.55 ml (63%) of N,N,N',N',2,2-hexamethyl-1,3-propanediamine: bp 162°; ir (neat) 2970, 2945, 2855, 2820, 2760 (s, CH), 1450 (m), 1375, 1350, 1300 (w), 1255, 1150 (m), 1120, 1100 (w), 1047 (s), and 847 cm^{-1} (m); pmr ($CDCl_3$) δ 0.88 (s, 6, CH_3C), 2.12 (s, 4, CH_2), and 2.27 ppm (s, 12, CH_3N); exact mass of parent ion, calcd 158.17826, found 158.17848.

Anal. Calcd for $C_9H_{22}N_2$: C, 68.29; H, 14.01; N, 17.70. Found: C, 68.11; H, 14.18; N, 17.90.

Although we have found no report of the synthesis or properties of this compound, its perchlorate has been patented for use as a propellant.[21]

o-Bis(dimethylaminomethyl)benzene.--Essentially the same procedure[21] described in the preceding section was applied to 19.3 g (0.098 mol) of 82% pure *o*-(dimethylaminomethyl)benzylamine to obtain 15.5 g of 86% pure (by glpc) *o*-bis(dimethylaminomethyl)benzene. Recrystallization of the hydrochloride and regeneration of the base gave 12.3 g of 95% pure material: bp 96--96.5° (8 mm); ir (neat) 3060, 3015 (w, aromatic CH), 2970, 2940, 2855, 2815 (s, sp^3-CH), 1450 (s, CH_2), 1350 (m, CH_3), 1300 (w), 1252, 1177 (m), 1152, 1100 (w), 1047 (m), 1027, 848, and 752 cm^{-1} (s); pmr ($CDCl_3$) δ 2.21 (s, 12.5, CH_3), 3.51 (s, 4.0, CH_2), and 7.0--7.5 ppm (m, 4.1, CH); monoperchlorate, white needles from H_2O, mp 188--189°.

Anal. of the monoperchlorate. Calcd for $C_{12}H_{21}N_2ClO_4$: C, 49.23; H, 7.23; Cl, 12.11. Found: C, 49.12; H, 7.16; Cl, 12.29.

Registry No.—**1**, 6159-17-7; 1 oxime (*Z*), 53369-67-8; 1 oxime (*E*), 53403-31-9; **2**, 53369-68-9; **2** hydrochloride, 53403-32-0; **3**, 10289-77-7; **4**, 53369-69-0; **5**, 53403-33-1; **6**, 53403-34-2; **7**, 53369-70-3; 2,2-dimethyl-3-dimethylaminopropanal, 15451-14-6; hydroxylamine hydrochloride, 5470-11-1; 2,2-dimethyl-3-dimethylaminopropanal oxime, 7405-24-5; 2,2-dimethyl-3-dimethylaminopropylamine, 53369-71-4; 2-(dimethylaminomethyl)cyclohexanone oxime, 53369-72-5; *cis*-2-(dimethylaminomethyl)cyclohexylamine, 53369-73-6; *trans*-2-(dimethylaminomethyl)cyclohexylamine, 53369-74-7; 2-methyl-3-dimethylaminopropylamine, 6105-72-2; 4-methyl-3,4-diazatricyclo[5.2.1.$0^{2,6}$]-2-decene, 53369-75-8; 3-methylene-2-norbornanone, 5597-27-3; methylhydrazine, 60-34-4; *o*-(dimethylaminomethyl)benzonitrile, 53369-76-9; *o*-cyanobenzyl bromide, 22115-41-9; dimethylamine, 124-40-3; *o*-(dimethylaminomethyl)benzylamine, 53369-77-0; *o*-(dimethylaminomethyl)-benzylamine hydrochloride, 53369-78-1; *N,N,N',N'*,2,2-hexamethyl-1,3-propanediamine, 53369-79-2; *o*-bis(dimethylaminomethyl)-benzene, 53369-80-5; *o*-bis(dimethylaminomethyl)benzene monoperchlorate, 53369-81-6.

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The Intrinsic Hydrophilic Character of Organic Compounds. Correlations in Terms of Structural Contributions[1]

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Log γ, where $\gamma = c_w/c_g$, with c_w being the concentration of a compound in dilute aqueous solution at 25° and c_g the concentration in the gas phase in equilibrium with the aqueous solution (both in moles per liter), is defined as the intrinsic hydrophilicity of a compound. Values for 292 compounds are listed, and parameters for a bond contribution correlation and a group contribution correlation are determined. Major deviations from the correlations arising from distant polar interactions (interactions between halogen, oxygen, nitrogen, or sulfur substituents separated by more than one carbon atom) are observed. The significance of such deviations and of the relative magnitudes of the group contributions is discussed.

The hydrophilic and hydrophobic character of compounds[2,3] is commonly discussed in terms of data on systems involving an aqueous phase and some other liquid phase. Such data, which include water solubilities and distribution coefficients between water and some other solvent,[4,5] have been quite useful. They depend on differences in free energy (or of enthalpy or some other property) of the molecules of a compound when they are surrounded by water molecules and when they are surrounded by molecules of the other solvent. Hence they depend not only on the nature of the compound in question and on the nature of water but also on the nature of the other solvent in the system in question. The interpretation of data may be simplified somewhat if we consider the difference in free energy of molecules of a given compound when they are surrounded by water and when they are surrounded by nothing, that is, when they are in the gas phase. We shall consider the tendency of a molecule to go from the gas phase to dilute aqueous solution to be a measure of its *intrinsic hydrophilic character*.

In order to discuss the relationship between molecular structure and the intrinsic hydrophilic character of compounds in quantitative terms we have carried out correlations in terms of structural additivity schemes. Such schemes have been used in correlations of enthalpies of formation, entropies, and other thermodynamic properties.[6-8] These correlations have been largely restricted to the properties of compounds in the gas phase. They would be more useful if they were extended to the common solvents in which most reactions are run. Such extensions would consist of correlations concerning transfer processes between the gas phase and the solvents of interest. Butler and coworkers pointed out long ago that the free energy of transfer of organic compounds from the gas phase to aqueous solution is an approximately additive function of the groups present in the compounds.[9-11] Pierotti, Deal, and Derr

treated about 340 cases, including 71 in which water was the solvent, by an empirical equation that may be applied to any compound in any solvent (when the appropriate parameters have been determined).[12] Although this equation is reasonably economical with parameters in its application to solvents, in general it is less so when applied to any one solvent. The 15 homologous series of compounds whose activity coefficients in water were correlated required 30 disposable parameters. A group contribution scheme of the Benson type[6,8] would cover all these compounds and many more with only 24 parameters. For this reason and because of the increased number of reliable data that have become available in recent years, we have correlated activity coefficients in the gas phase relative to aqueous solution using both a bond contribution and a group contribution scheme. Not only will such correlations aid in understanding hydrophobic bonding[2,3] and in predicting equilibrium constants for chemical reactions, they will also be useful in studies of the loss of flavor components from largely aqueous foods,[13] the transfer of pesticides and other compounds between various bodies of water and the atmosphere, and in other ways. In addition, when either the vapor pressure or the water solubility of a difficultly soluble organic compound is known, the other may be estimated from such correlations.

Results

We have tried to correlate values of log γ for various compounds, where γ is the activity coefficient in the ideal gas phase relative to infinitely dilute aqueous solution. As shown in eq 1, γ is taken to be equal to the concentration of

$$\gamma = c_w/c_g \quad (1)$$

the compound in a dilute aqueous solution divided by its concentration in the gas phase that is in equilibrium with that solution. When the compound and water are not very soluble in each other, c_w may be taken as the water solubility and c_g as the vapor pressure of the compound. We have made γ dimensionless by expressing c_w and c_g in moles per liter. Data at 25° were used and water solubilities were used only for compounds whose water solubility is 1.0 *M* or less, except for ethyl formate (1.2 *M*).

The values of log γ, log c_w, log c_g, and P (where P is the vapor pressure in millimeters; log c_g = log P − 4.269) we used and the appropriate literature references are listed in Table IV.[14] The values of γ cover a range of about 10^{10}.

The bond contribution scheme used is similar to that of Benson and Buss, in which certain groups such as cyano, nitro, and carbonyl are treated as atoms. Thus the contribution of the C–CN bond includes implicitly the contribution of the carbon–nitrogen triple bond of the cyano group, and the H–CO bond contribution includes half the contribution of the carbon–oxygen double bond. Olefinic, acetylenic, and aromatic carbon are denoted C_d, C_t, and C_{ar}, respectively. The contribution for a C_d–H bond (or for any C_d–X bond) includes one-fourth of the contribution for the carbon–carbon double bond, and any C_t–X contribution contains half the triple bond contribution. However, the C_{ar}–H contribution does not include a C_{ar}=C_{ar} contribution. The latter was kept separate so as to simplify the treatment of data on nonbenzenoid aromatic compounds. For example, log γ for naphthalene is equal to eight times the C_{ar}–H contribution plus 11 times the C_{ar}=C_{ar} contribution, and log γ for pyridine is equal to five times the C_{ar}–H contribution plus four times the C_{ar}=C_{ar} and two times the C_{ar}=N_{ar} contribution. The 34 bond contributions obtained by least-squares treatment of data on 263 compounds are listed in Table I. The 263 values of log γ calculated from these contributions, which are listed in Table IV,[14] differed from the experimental values with a standard deviation of 0.41. The deviations from about 40 additional values of log γ, some of which had not been located when the parameters listed in Table I were calculated but some of which had been left out of the least-squares treatment because of their highly deviant nature, tended to be larger than this. Most of the larger deviations were of the types that will be rationalized in our discussion of the group contribution correlation.

Table I
Bond Contributions to the Logarithms of Activity Coefficients in the Gas Phase Referred to Aqueous Solution[a]

Bond[b]	Contribution	Bond	Contribution
C–H	−0.11	C_{ar}–Br	0.21
C–F	−0.50	C_{ar}–NO_2[c]	1.83
C–Cl	0.30	C_{ar}–O	−0.74
C–Br	0.87	C_{ar}–S	0.53
C–I	1.03	C_{ar}–CO[d]	1.14
C–CN[c]	3.28	C_{ar}=C_{ar}[e]	0.33
C–NO_2[c]	3.10	C_{ar}=N_{ar}[e]	1.64
C–O	1.00	C_d–H	−0.15[f]
C–S	1.11	C_d–Cl	0.16[f]
C–N	1.35	C_d–C_d	0.48[f]
C–C	0.04	C_d–CO[d]	2.42[f]
C–CO[d]	1.78	C_t–H[g]	0.00
C–C_d	0.15[f]	CO–H[d]	1.19
C–C_t[g]	0.64	CO–O[d]	0.28
C–C_{ar}	0.11	O–H	3.21
C_{ar}–H	−0.21	S–H	0.23
C_{ar}–Cl	−0.14	N–H	1.34

[a] At 25°. [b] C without a subscript refers to a carbon atom bound by single bonds to four other atoms except in CN. [c] The cyano and nitro groups are treated as univalent atoms. [d] The CO group is treated as a divalent atom. [e] The bond denoted = is the $\sigma + \pi$ bond in an aromatic ring. [f] This contribution includes one-fourth the contribution of the carbon–carbon double bond(s). [g] This contribution includes one-half the contribution of the carbon–carbon triple bond.

The group contribution scheme we used is similar to that of Benson and coworkers.[6,8] In most cases a group is taken to contain one polyvalent atom and the monovalent atoms bonded to it, but the group is *characterized* by the nature of the atoms to which it is attached as well as those it contains. Thus a methylene group attached to two oxygen atoms is different from one attached to a carbon and an oxygen atom. Our notation for group contributions, which is $[CH_2(O)_2]$ and $[CH_2(C)(O)]$ for the two groups just referred to, for example, differs from that of Benson and coworkers in that the atoms contained in the group are not parenthesized. We feel that the notation $[C(H)_2(O)_2]$ makes it less obvious that additional contributions are required for the oxygen atoms but not for the hydrogen atoms. The value of log γ for methyl ethyl ether, for example, is taken to be the sum of the four contributions $[CH_3(O)]$, $[O(C)_2]$, $[CH_2(C)(O)]$, and $[CH_3(O)]$. Instead of the symbol C_B for benzenoid carbon[6,8] we have used C_{ar} to include the carbon atoms in the rings of polynuclear aromatic and certain hetaromatic compounds as well. For example, log γ for pyridine is set equal to $3[C_{ar}H(C_{ar})_2] + 2[C_{ar}H(C_{ar})(N_{ar})] + [N_{ar}(C_{ar})_2]$. As in the case of the bond contribution scheme, C_d and C_t refer to olefinic and acetylenic carbon, respectively. Since any C_d must be attached to another C_d and any C_t to another C_t, the C_d or C_t at the other end of the multiple bond is not included in the nota-

Table II
Group Contributions to the Logarithms of Activity Coefficients in the Gas Phase Referred to Aqueous Solution[a]

Group	Contribution	Group	Contribution
$CH_3(X)$[b]	−0.62	$C(C)_3(O)$	0.78
$CH_2(C)_2$	−0.15	$CH_2(O)_2$	−2.54
$CH(C)_3$	0.24	$CH(C)(O)_2$	−1.35[c]
$C(C)_4$	0.71	$CH_2(C_d)(O)$	−0.57[c]
$CH_2(C)(C_{ar})$	−0.19	$CH_2(C)(CO)$	−0.15
$CH(C)_2(C_{ar})$	0.29	$C_{ar}(O)(C_{ar})_2$	−0.43
$C(C)_3(C_{ar})$	0.93	$C_{ar}(CO)(C_{ar})_2$	−0.84[c]
$CH_2(C)(C_d)$	−0.23	$C_dH(CO)$	0.28
$CH_2(C_d)_2$	−0.31[c]	CHO(Y)[f]	3.23
$CH_2(C)(C_t)$	−0.29[d]	$CO(C)_2$	4.03
C_dH_2	−0.41	$CO(C)(C_{ar})$	4.26[c]
$C_dH(C)$	0.22	CO(C)(O)	4.09
$C_d(C)_2$	0.67	$CO(C_{ar})(O)$	4.57[c]
$C_dH(C_d)$	0.18	$CH_2(C)(S)$	−0.02
$C_d(C)(C_d)$	0.86	$C_{ar}(S)(C_{ar})_2$	−0.25[c]
C_tH	0.00[d]	$CH_2(C)(N)$	−0.08
$C_t(C)$	0.96[d]	$CH_2CN(C)$[g]	3.43
$C_{ar}H(C_{ar})_2$	0.11	$CH_2NO_2(C)$[g]	3.27
$C_{ar}(C)(C_{ar})_2$	0.70	$CHNO_2(C)_2$[g]	3.53[c]
$C_{ar}(C_{ar})_3$[e]	0.47	$C_{ar}H(C_{ar})(N_{ar})$	0.11[h]
$CHF_2(C)$	0.70[c]	$C_{ar}(C)(C_{ar})(N_{ar})$	0.59
$CH_2Cl(C)$	1.05	$C_{ar}NO_2(C_{ar})_2$[g]	2.19
$CHCl_2(C)$	1.33	OH(C)	4.45
$CCl_3(C)$	0.80[c]	$OH(C_{ar})$	4.45[i]
$CHCl(C)_2$	1.46	$O(C)_2$	2.93
$CH_2Cl(C_d)$	0.61[c]	$O(C)(C_{ar})$	1.25[c]
C_dHCl	0.05[c]	O(C)(CO)	−0.53
$C_{ar}Cl(C_{ar})_2$	0.18[c]	SH(C)	1.56
$CH_2Br(C)$	1.10	$SH(C_{ar})$	1.56[j]
$CHBr(C)_2$	1.58[c]	$S(C)_2$	2.35
$C_{ar}Br(C_{ar})_2$	0.49	$S(C)(C_{ar})$	2.30[c]
$CH_2I(C)$	1.14	$NH_2(C)$	4.15
$CHI(C)_2$	1.57[c]	$NH(C)_2$	4.37
$CH_2(C)(O)$	−0.13	$N(C)_3$	4.14
$CH(C)_2(O)$	0.12	$N_{ar}(C_{ar})_2$	3.06

[a] At 25°. [b] X is C, O, N, CO, C_d, C_{ar}, C_t, or S. [c] Based on only one log γ value. [d] This is one of a set of contributions whose sum was determined by a considerably larger set of log γ values but for which only the minimum number of log γ values required for separation into individual contributions was available. [e] This refers to a carbon atom common to two fused aromatic rings, such as C-9 in naphthalene. It may not be applicable to the carbon atoms joined by single bonds in biphenyl, for example. [f] Y is C, O, C_d, or C_{ar}. [g] Nitro and cyano groups are treated as univalent atoms. [h] Assigned the same value as $[C_{ar}H(C_{ar})_2]$. [i] Assigned the same value as [OH(C)]. [j] Assigned the same value as [SH(C)].

tion for the group contribution. Thus the contribution of an olefinic methylene group is written $[C_dH_2]$ rather than $[C_dH_2(C_d)]$.

The values of certain group contributions must be assigned arbitrarily.[6,8] Most such assignments were made in the same way used by Benson and coworkers; *e.g.*, $[CH_3(O)]$, $[CH_3(CO)]$, $[CH_3(N)]$, etc., were all assigned the same value as $[CH_3(C)]$. We also followed their practice of treating certain groups, such as cyano, nitro, and carbonyl, as if they were atoms.

Many of the deviations observed in the bond contribution correlation may be thought of as arising from interactions between polar bonds. When the polar bonds involve a common atom, such interactions are included automatically in a group contribution. The interaction between the two carbon–oxygen bonds involving the central carbon atom of methylal, for example, is included in the $[CH_2(O)_2]$ group contribution. However, early regression analyses convinced us that interactions between more widely separated polar bonds were producing marked deviations from our group contribution correlation. To ignore such interactions would reduce the quality of our correlation and make the values of the parameters depend significantly on the particular set of compounds for which log γ values were available. We therefore decided to obtain contributions for such distant polar interactions or to neglect data upon which such interactions might have a significant effect. Most distant polar interactions of a given type appeared in only one of the 292 compounds for which we had log γ values. Also, a number of group contributions appeared in sets of compounds no larger than the number of parameters to be determined. Compounds of either of these types were deleted from the set before the regression analysis because the analysis would be trivial in such cases. Analysis of the remaining 212 log γ values gave two distant interaction parameters and 49 group contributions (not counting some assigned arbitrarily). From these parameters the log γ values may be calculated with a standard deviation of 0.12, which may not be very much larger than the average experimental uncertainty. The 49 group contributions are listed in Table II with the contributions assigned arbitrarily and 20 additional contributions calculated from data that had not been included in the least-squares treatment. Since these latter contributions are based on small sets of log γ values of the same size as the set of contributions being determined (the set size being 1.0 in most cases), they are less reliable than those obtained from the overdetermined system.

Table III
Distant Polar Interactions in Various Types of Compounds[a]

Compound(s)	Interaction	Compound	Interaction
Pyrazines	−2.26	*cis*-CHCl=CHCl	0.76
RO–C–C–OR	−1.58	$ClCH_2CH_2Br$	−0.72
$HOCH_2CH(OH)CH_2OH$	−7.05	$BrCH_2CH_2Br$	−0.66
$HOCH_2CH_2OH$	−3.02	$MeCHBrCH_2Br$	−0.65
$(ClCH_2CH_2)_2S$	−1.53	$BrCH_2CH_2CH_2Br$	−0.61
p-$HOC_6H_4NO_2$	1.12	$ClCH_2CH_2CH_2Cl$	−0.57
Cl_3CCHCl_2	−1.12	Cl_3CCCl_3	−0.56
$H_2NCH_2CH_2NH_2$	−1.00	*trans*-CHCl=CHCl	0.46
$MeCHClCH_2Cl$	−0.98	*p*-$C_6H_4Br_2$	0.27
Cl_2CHCH_2Cl	−0.95	*p*-HOC_6H_4Br	0.26
$Cl_2CHCHCl_2$	−0.92	*o*-$C_6H_4Cl_2$	0.19
p-HOC_6H_4CHO	0.83	*m*-$C_6H_4Cl_2$	−0.09
$ClCH_2CH_2Cl$	−0.83	*p*-$C_6H_4Cl_2$	−0.07

[a] Values of $(\log \gamma)_{obsd} - (\log \gamma)_{calcd}$, with the latter being obtained from the group contribution scheme.

The only distant polar interactions (numbers that must be added to the group contributions to obtain log γ values) that appeared in more than one compound, and hence the only ones calculated by a least-squares treatment, were the interaction of the two nitrogen atoms in a pyrazine ring and the interaction of two alkoxy groups attached to adjacent saturated carbon atoms. These are the first two entries in Table III. The other distant polar interactions or sets of distant polar interactions occurred in only one compound each and are therefore listed with the formula of the compound in Table III.

Most of the larger interactions seem qualitatively understandable in terms of the structures of the compounds involved. Glycerol and ethylene glycol are internally hydro-

gen bonded in the gas phase. Hence their hydroxy groups do not gain as much hydrogen bonding on going into aqueous solution and their log γ values are smaller than would be expected from [OH(C)] and [CH_2(C)(O)] values derived from data on monohydroxylic alcohols, for which internal hydrogen bonding is impossible. The third largest interaction, that found in pyrazines, may also be explained in terms of hydrogen bonding, which we assume is the main reason that pyridine and most other azines are much more water soluble than benzene. That is, the large positive value of [$N_{ar}(C_{ar})_2$] listed in Table II, which arises from data on pyridine derivatives, is a reflection of the ability of the pyridine nitrogen atom to accept hydrogen bonds from water. The hydrogen-bonding ability of these nitrogen atoms, like that of other basic atoms of a given type, is known to be decreased by electron-withdrawing substituents.[15] The value of log K for hydrogen bonding of 3- and 4-substituted pyridines to p-fluorophenol in carbon tetrachloride at 25° decreases by 0.24 for each pK unit by which the basicity in water at 25° decreases.[15] Each nitrogen atom in pyrazine is about 4.8 pK units more weakly basic than the nitrogen atom in pyridine.[16] These numbers seem large enough to make it plausible that weak hydrogen bonding to the two nitrogen atoms of pyrazines (relative to hydrogen bonding to the nitrogen atom of pyridine) accounts for much of the distant polar interaction listed for pyrazines. A qualitatively similar effect would be expected for ethylenediamine, but since the amino groups in ethylenediamine are only about 1.0 pK unit weaker than the one in ethylamine[16] it is not surprising that the distant polar interaction is smaller than for pyrazines. The interactions for β-diethers and for the saturated polyhalides and 2,2′-dichlorodiethyl sulfide may be rationalized qualitatively in the same way. Interpretation of the relative magnitudes of these interactions is probably complicated by the following facts. (1) Some of the halides are probably of such low basicity that they are so little involved in hydrogen bonding with water that further decreases in basicity have little effect. (2) Some of the compounds, such as those with dichloromethyl groups, may be acidic as well as basic participants in hydrogen bonding. (3) The strength of hydrogen bonding depends on the polarity as well as the acidity and basicity of the interacting species. (4) Some of the interactions listed may contain major experimental errors.

The largest positive distant polar interaction, for p-nitrophenol, is probably also attributable largely to hydrogen-bonding effects. The nitro group probably interacts with water largely by acting as a base in hydrogen bonding. With the hydroxy group, however, hydrogen bonding to water with the group acting as an acid must be important. The p-hydroxy substituent acts as an electron donor and increases the basicity of the nitro group and the p-nitro substituent acts as an electron withdrawer and increases the acidity of the hydroxy group. Thus the nitro and hydroxy groups in p-nitrophenol may interact more strongly with water than do the nitro and hydroxy groups in nitrobenzene and phenol, respectively. The same argument explains the smaller but still positive interaction observed with p-hydroxybenzaldehyde.

We do not understand why the interactions listed for the 1,2-dichloroethylenes are positive (although the value for the more polar cis isomer would be expected to be more positive, as observed).

Intrinsic hydrophilic character is more simply understood in terms of molecular structure than is the hydrophilic character measured by water solubility or distribution coefficients. Since a hydroxy group can participate as both an acid and a base in hydrogen bonding whereas an ethereal oxygen atom can participate only as a base, alcohols should ordinarily be considerably more hydrophilic than isomeric ethers. In agreement with expectation γ for n-butyl alcohol is more than 100 times as large as γ for its isomer diethyl ether. In contrast, the solubilities of the two compounds differ by less than 20%; n-butyl alcohol is already so strongly hydrogen bonded in the organic phase that it does not gain as much hydrogen bonding on going into aqueous solution as it otherwise would.

Although the relative magnitudes of the group contributions in Table II tend to agree with common notions concerning structural effects on hydrophilic character, with the contributions for oxygen- and nitrogen-containing groups tending to be larger than those for hydrocarbon groups, it should be remembered that some of the numbers are the results of arbitrary assignments. In the following discussion we shall consider only points that are independent of such assignments. Some of the contributions reflect the kind of polar interactions already discussed in connection with Table III. For example, although [CH_2(C)(O)] is essentially equal to [$CH_2(C)_2$], [$CH_2(O)_2$] is more than two units smaller. Each of the two atoms lowers the basicity and, hence, the hydrogen-bonding ability of the other. Neither of the oxygen atoms is *in* the $CH_2(O)_2$ group, as the carbon and hydrogen atoms are, but since the $CH_2(O)_2$ is the only group uniquely characteristic of a compound with two oxygen atoms bonded to the same methylene group, the interaction appears in the [$CH_2(O)_2$] contribution.

The fact that [S(C)(C_{ar})] is about equal to [$S(C)_2$] whereas [O(C)(C_{ar})] is considerably smaller than [$O(C)_2$] reflects the much greater ability of a phenyl group to withdraw electrons, by a resonance interaction, from an oxygen atom to which it is bonded than from a sulfur atom. The fact that [O(C)(CO)] is still smaller than [O(C)(C_{ar})] reflects the greater electron-withdrawing power of a carbonyl group.

In applying the group contributions in Table II to compounds in which significant distant polar interactions seem possible, the magnitudes of such interactions may be estimated from the interactions listed in Table III. Although the group contribution scheme is to be preferred when the required group contributions have been (or can be) determined, the less precise bond contribution scheme presently covers a significantly larger number of possible compounds.

A brief and preliminary account of this investigation will appear in a forthcoming book.[17]

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Table IV. Experimental and Calculated Activity Coefficients in the Gas Phase Referred to Dilute Aqueous Solution at 25°.

	Compound	P(mm)[a]	-log c_g[b]	Ref.[c]	-log c_w[d]	Ref.[c]	log γ[e] Exptl	Group	Bond
1.	Methane	760	1.39		2.82	(1-4)	-1.43	f	-0.43
2.	Ethane	760	1.39		2.70	(1-4)	-1.31	-1.23	-0.60
3.	Propane	760	1.39		2.85	(1-4)	-1.46	-1.38	-0.78
4.	n-Butane	760	1.39		2.97	(1-4)	-1.58	-1.52	-0.95
5.	2-Methylpropane	760	1.39		3.07	(1,3)	-1.68	-1.61	-0.95
6.	n-Pentane	512.5	1.56	(6b,7,21)	3.27	(1-3,5,8)	-1.71	-1.67	-1.13
7.	2,2-Dimethylpropane	760	1.39		3.34	(1,3)	-1.95	-1.76	-1.13
8.	Cyclopentane	317.5	1.77	(6a,21)	2.65	(1,3,5)	-0.88	-0.73	-0.87
9.	n-Hexane	151.3	2.09	(6b,7,21)	3.96	(1-3,5,8)	-1.87	-1.81	-1.30
10.	2-Methylpentane	211.8	1.94	(6b,7,21)	3.79	(1,3,5)	-1.85	-1.90	-1.30
11.	3-Methylpentane	189.8	1.99	(6b,7,21)	3.83	(1,5)	-1.84	-1.90	-1.30
12.	Cyclohexane	97.58	2.28	(6a,7,21)	3.18	(1,3,5)	-0.90	-0.87	-1.05
13.	Methylcyclopentane	137.5	2.13	(6a,7,21)	3.30	(1)	-1.17	-0.95	-1.05
14.	2,2-Dimethylbutane	319.1	1.77	(6b,7,21)	3.67	(1,3)	-1.90	-1.90	-1.30
15.	n-Heptane	45.81	2.61	(6b,7,21)	4.53	(1-3,5,8)	-1.92	-1.96	-1.47
16.	2,4-Dimethylpentane	98.40	2.28	(6b,7,21)	4.39	(1,3,5)	-2.11	-2.12	-1.47
17.	Methylcyclohexane	46.33	2.60	(6a,7,21)	3.85	(1,3,5)	-1.25	-1.10	-1.22
18.	n-Octane	14.04	3.12	(6b,7,21)	5.24	(1-3,5,8)	-2.12	-2.10	-1.65
19.	2,2,4-Trimethylpentane	49.34	2.58	(6b,7,21)	4.67	(1)	-2.09	-2.28	-1.65
	Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
20.	cis-1,2-Dimethylcyclohexane	14.47	3.11	(6a,7,21)	4.27	(1)	-1.16	-1.33	-1.40
21.	Ethylene	760	1.39		2.33	(1,2)	-0.94	-0.82	-0.59
22.	Propylene	760	1.39		2.32	(1-3)	-0.93	-0.81	-0.61
23.	1-Butene	760	1.39		2.40	(1,3)	-1.01	-1.03	-0.79
24.	2-Methylpropene	760	1.39		2.33	(1,3)	-0.94	-0.97	-0.64
25.	1-Pentene	648.8	1.46	(6b,7,21)	2.68	(1,5)	-1.22	-1.18	-0.96
26.	trans-2-Pentene	505.5	1.56	(6b,7)	2.54	(1,3,5)	-0.98	-1.02	-0.81
27.	Cyclopentene	380.2	1.69	(6a)	2.10	(1,5)	-0.41	-0.16	-0.56
28.	2-Methyl-2-butene	466.1	1.60	(6b,7,21)	2.56	(3)	-0.96	-0.95	-0.66
29.	3-Methyl-1-butene	760	1.39		2.73	(1)	-1.34	-1.41	-0.96
30.	1-Hexene	187.2	2.00	(6b,7,21)	3.23	(1,3,5)	-1.23	-1.32	-1.14
31.	Cyclohexene	88.83	2.32	(6a,21)	2.99	(1,3,5)	-0.27	-0.30	-0.73
32.	4-Methyl-1-pentene	268	1.84	(6b)	3.24	(5)	-1.40	-1.42	-1.14
33.	trans-2-Heptene	46.55	2.60	(6b,7,21)	3.82	(1,3,5)	-1.22	-1.31	-1.16
34.	1-Methylcyclohexene	30.61	2.78	(6a)	3.27	(1)	-0.49	-0.48	-0.76
35.	1-Octene	17.38	3.03	(6b,7)	4.62	(1,5)	-1.59	-1.61	-1.48
36.	1,3-Butadiene	760	1.39		1.87	(1,3)	-0.41	-0.46	-0.40
37.	1,4-Pentadiene	734.3	1.40	(6b,7,21)	2.09	(1,5)	-0.69	g	-0.80
38.	2-Methyl-1,3-butadiene	550	1.53	(6b,7)	2.03	(1)	-0.50	-0.40	-0.42
39.	1,5-Hexadiene	208	1.95	(6b,7)	2.69	(1,5)	-0.74	-0.83	-0.97
40.	2,3-Dimethyl-1,3-butadiene	143.8	2.11	(6b)	2.40	(3)	-0.29	-0.34	-0.45
	Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
41.	Acetylene	760	1.39		1.38	(2,3)	0.01	g	-0.01
42.	Propyne	760	1.39		1.04	(1,3)	0.35	g	0.31
43.	1-Butyne	760	1.39		1.27	(1,3)	0.12	0.05	0.14
44.	1-Pentyne	431.4	1.63	(6b)	1.64	(1,5)	-0.01	-0.08	-0.03
45.	1-Hexyne	136.0	2.14	(6b)	2.35	(1,5)	-0.21	-0.25	-0.21
46.	1-Heptyne	52.51	2.55	(6b)	2.99	(1,5)	-0.44	-0.38	-0.39
47.	1-Octyne	13.60	3.14	(6b)	3.66	(1,5)	-0.52	-0.52	-0.56
48.	1-Nonyne	6.26	3.47	(6b)	4.24	(1,5)	-0.77	-0.67	-0.74
49.	Benzene	95.18	2.29	(6a,7,21)	1.64	(1-5)	0.65	0.67	0.67
50.	Toluene	28.44	2.81	(6a,7,21)	2.25	(1-5)	0.56	0.64	0.68
51.	Ethylbenzene	9.57	3.29	(6a,7,21)	2.84	(1-5)	0.45	0.45	0.51
52.	o-Xylene	6.69	3.44	(6a,7,21)	2.78	(1-3,5)	0.66	0.62	0.69
53.	m-Xylene	8.36	3.35	(6a,7,21)	2.76	(2,3)	0.59	0.62	0.69
54.	p-Xylene	8.82	3.32	(6a,7,21)	2.73	(2,3)	0.59	0.62	0.69
55.	Propylbenzene	3.43	3.73	(6a,7,21)	3.34	(1-3,5)	0.39	0.31	0.33
56.	2-Propylbenzene	4.66	3.60	(6a,7,21)	3.38	(1-3)	0.22	0.32	0.33
57.	1,2,4-Trimethylbenzene	2.10	3.95	(6a,7,21)	3.32	(1,5)	0.63	0.59	0.70
58.	Butylbenzene	1.08	4.23	(6a,7,21)	3.94	(1-3)	0.29	0.16	0.16
59.	2-Butylbenzene	1.88	4.00	(6a,7,21)	3.67	(1-3)	0.33	0.17	0.16
60.	t-Butylbenzene	2.21	3.92	(6a,7,21)	3.60	(1-3)	0.32	0.34	0.16
61.	t-Amylbenzene	0.97	4.28	(6a,7)	4.15	(2,3)	0.13	0.20	-0.02
62.	Naphthalene	0.084	5.34	(25,6a,7)	3.57	(6a,2,3)	1.77	1.84	1.89
	Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
63.	Acenaphthene	0.0024	6.89	(24)	4.40	(2)	2.49	2.63	2.16
64.	Anthracene		9.40[h]	(23)	6.35	(2,3)	3.14	3.01	3.11
65.	Phenanthrene		8.05[h]	(23)	5.05	(2,4)	2.98	3.01	3.11
66.	Fluoromethane	760	1.39		1.23	(3,22)	0.16	f	-0.82
67.	Trifluoromethane	760	1.39		1.98	(3)	-0.59	f	-1.62
68.	Tetrafluoromethane	760	1.39		3.71	(3)	-2.32	f	-2.02
69.	Chloromethane	760	1.39		1.00	(3,22)	0.39	f	-0.02
70.	Dichloromethane	411.2	1.66	(7,21)	0.63	(2,3)	1.03	f	0.39
71.	Trichloromethane	202.8	1.96	(7,21)	1.21	(2,3,5)	0.75[i]	f	0.80
72.	Tetrachloromethane	109.6	2.23	(6c,7,21)	2.30	(2,3)	-0.07	f	1.21
73.	Bromomethane	760	1.39		0.81	(3,22)	0.58	f	0.55
74.	Dibromomethane	44.11	2.62	(7,21)	1.18	(2,3)	1.44	f	1.53
75.	Tribromomethane	6.25	3.47	(7,21)	1.91	(2,3)	1.56	f	2.51
76.	Iodomethane	405.9	1.65	(6c,7,21)	1.00	(2,3,5,22)	0.65	f	0.71
77.	Chlorofluoromethane	760	1.39		0.82	(3)	0.57	f	-0.42
78.	Chlorodifluoromethane	760	1.39		1.47	(3)	-0.08	f	-0.81
79.	Chlorotrifluoromethane	760	1.39		3.24	(3)	-1.85	f	-1.21
80.	Dichlorodifluoromethane	760	1.39		2.63	(3)	-1.24	f	-0.40
81.	Bromotrifluoromethane	760	1.39		2.70	(3)	-1.31	f	-0.64
82.	1,1-Difluoroethane	760	1.39		1.31	(3)	0.08	g	-1.40
83.	Chloroethane	760	1.39		0.93	(2,3,5)	0.46	0.44	-0.19
84.	Bromoethane	474.5	1.59	(7,21)	1.08	(2,3,5)	0.51	0.48	0.38
	Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
85.	Iodoethane	136.2	2.13	(6c,7,21)	1.60	(2,3,5)	0.53	0.53	0.54
86.	1,1-Dichloroethane	229.8	1.91	(7,21)	1.29	(2,3)	0.62	0.71	0.22
87.	1,2-Dichloroethane	85.62	2.33	(7,21)	1.06	(2,3)	1.27	2.10[j]	0.22
88.	1,2-Dibromoethane	11.40	3.21	(7,21)	1.67	(2,3)	1.54	2.20[j]	1.35
89.	1-Chloro-2-bromoethane	33.1	2.75	(7,21)	1.52	(2,3)	1.43	2.15[j]	0.79
90.	1,1,1-Trichloroethane	120.7	2.19	(6c,7,21)	2.01	(3,2)	0.18	g	0.63
91.	1,1,2-Trichloroethane	24.13	2.89	(6c,7,21)	1.46	(2,3)	1.43	2.38[j]	0.63
92.	1,1,2,2-Tetrachloroethane	5.95	3.49	(6c,7,21)	1.76	(3)	1.73[i]	2.65[j]	1.04[k]
93.	Pentachloroethane	4.54	3.61	(7,21)	2.61	(3)	1.00	2.12[j]	1.45
94.	Hexachloroethane	0.367	4.70	(7,21)	3.67	(3)	1.03	1.59[j]	1.86
95.	2-Chloro-1,1,1-trifluoroethane	760	1.39		1.45	(3)	-0.04	l	-1.38
96.	1,1,2,2-Tetrachlorodifluoroethane	47.8	2.59	(21)	3.19	(3)	-0.60	l	0.24
97.	1,1,2-Trichlorotrifluoroethane	340	1.74	(21)	3.04	(3)	-1.30	l	-0.56
98.	1,1-Dichlorotetrafluoroethane	760	1.39		3.23	(3)	-1.84	l	-1.37
99.	1,2-Dichlorotetrafluoroethane	760	1.39		3.09	(3)	-1.70	l	-1.37
100.	Chloropentafluoroethane	760	1.39		3.49	(3)	-2.10	l	-2.18
101.	1-Chloropropane	348.8	1.72	(7,21)	1.46	(2,3,5)	0.26	0.29	-0.37

Table IV (Continued)

	Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
102.	2-Chloropropane	482.1	1.59	(7,21)	1.41	(2,3,5)	0.18	0.25	-0.37
103.	1-Bromopropane	143.7	2.11	(7,21)	1.70	(2,3,5)	0.41	0.34	0.20
104.	2-Bromopropane	213.6	1.94	(7,21)	1.59	(2,3,5)	0.35	g	0.20
105.	1-Iodopropane	43.09	2.63	(6c,7,21)	2.20	(2,3,5)	0.43	0.38	0.36
106.	2-Iodopropane	69.01	2.43	(6c,7,21)	2.09	(2,3)	0.34	g	0.36
107.	1,2-Dichloropropane	53.61	2.53	(7,21)	1.61	(2,3)	0.92	1.90[j]	0.04
108.	1,3-Dichloropropane	18.25	3.01	(6c,7,21)	1.62	(2,3,5)	1.39	1.96[j]	0.04
109.	1,2-Dibromopropane	5.16	3.56	(6c,7,21)	2.14	(3)	1.42	2.07[j]	1.18
110.	1,3-Dibromopropane	1.36	4.14	(6c,7,21)	2.70	(3)	1.44	2.05[j]	1.18
111.	1-Chlorobutane	106.3	2.24	(21,7)	2.14	(3)	0.10	0.14	-0.54
112.	1-Bromobutane	41.27	2.66	(6c,7,21)	2.36	(2,3,5)	0.30	0.19	0.03
113.	1-Bromo-2-methylpropane	69.02	2.43	(6c,21)	2.44	(3,2)	0.02	0.11	0.03
114.	1-Iodobutane	13.86	3.13	(6c,7,21)	2.94	(2,3,5)	0.19	0.24	0.19
115.	1,1-Dichlorobutane	22.83	2.91	(6c,21)	2.40	(3)	0.51	0.42	-0.13
116.	1-Chloropentane	31.07	2.78	(6c,21)	2.73	(3)	0.05	0.00	-0.72
117.	2-Chloropentane	48.66	2.58	(6c,21)	2.63	(3)	-0.05	-0.06	-0.72
118.	3-Chloropentane	46.77	2.60	(6c,21)	2.63	(3)	-0.03	-0.06	-0.72
119.	1-Bromo-3-methylbutane	34.62	2.73	(6c,21)	2.88	(3)	-0.15	-0.03	-0.15
120.	Chloroethylene	760	1.39		1.75	(3)	-0.36	g	-0.28
121.	cis-1,2-Dichloroethylene	202.7	1.96	(7,21)	1.10	(3,2)[i]	0.86	0.10[j]	0.02
122.	trans-1,2-Dichloroethylene	330	1.75	(7,21)	1.19	(3,2)	0.56	0.10[j]	0.02
	Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
123.	Trichloroethylene	74.31	2.40	(6b,7,21)	2.08	(3,2)	0.32	l	0.32
124.	Tetrachloroethylene	18.47	3.00	(6b,7,21)	3.04	(3)	-0.04	l	0.63
125.	3-Chloropropene	366.8	1.70	(6c,21)	1.28	(3)	0.42	g	-0.20
126.	Chlorobenzene	12.1	3.18	(7,21)	2.44	(2,3,5)	0.74	g	0.75
127.	Bromobenzene	4.18	3.65	(6a,7,21)	2.58	(3,2)	1.07	1.05	1.10
128.	1,2-Dichlorobenzene	1.78	4.01	(7,21)	3.01	(2,3,5)	1.00	0.81[j]	0.82
129.	1,3-Dichlorobenzene	2.92	3.80	(7,21)	3.08	(2,3,5)	0.72	0.81[j]	0.82
130.	1,4-Dichlorobenzene	1.76	4.02	(7,21)	3.28	(2,3,5)	0.74	0.81[j]	0.82
131.	1,4-Dibromobenzene	0.052	5.76	(6a,7,21)	4.07	(3)	1.69	1.42[j]	1.53
132.	p-Bromotoluene	1.15	4.21	(6a,7,21)	3.19	(3)	1.02	1.02	1.11
133.	1-Bromo-2-ethylbenzene	0.531	4.54	(6a,21)	3.67	(3)	0.87	0.83	0.93
134.	o-Bromocumene	0.290	4.81	(6a,21)	4.19	(3)	0.62	0.69	0.76
135.	Dimethyl ether	760	1.39		0.00	(10,35)	1.39	1.70	1.37
136.	Dimethyl sulfide	484.9	1.58	(6c,10,21)	0.45	(10)	1.13	1.11	1.59
137.	Dimethoxymethane					(35)	2.15	2.09	3.12[k]
138.	1,3-Dioxolane					(30)	3.00	3.06	3.58[k]
139.	Diethyl ether					(31,35)	1.28	1.44	1.02
140.	Diethyl sulfide	58.37	2.50	(6c,21)	1.45	(2)	1.05	1.07	1.24
141.	Methyl propyl ether	454.6	1.60	(7,21)	0.38	(2,5)	1.22	1.42	1.02
142.	Methyl isopropyl ether	570	1.51	(7,15,21)	0.04	(35,2,5)	1.47	1.20	1.02[k]
143.	Tetrahydrofuran					(30,31)	2.54	2.36	1.24[k]
144.	1,4-Dioxane					(30)	3.70	3.76	3.20[k]
	Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
145.	Ethyl propyl ether	178	2.02	(12b,21)	0.69	(12b)	1.33	1.29	0.91[k]
146.	Methyl t-butyl ether					(33)	1.62	1.24	0.91[k]
147.	2-Methyltetrahydrofuran					(30)	2.42	2.01	1.06[k]
148.	Tetrahydropyran					(30)	2.29	2.23	1.06[k]
149.	Dipropyl ether	65.0	2.46	(12b,7,21)	1.61	(12b,2,5)	0.85	1.15	0.62
150.	Diisopropyl ether	151	2.09	(7,21)	1.70	(10)	0.59	0.71	0.62
151.	1,2-Diethoxyethane	33.75	2.74	(7,21)	0.15	(2)	2.59	2.53	2.64
152.	1,1-Diethoxyethane	34.61	2.73	(7,21)	0.33	(2)	2.40	g	2.64
153.	Di-n-butyl ether					(35,7)	0.61	0.83[k]	0.26[k]
154.	Anisole	4.16	3.64	(13,21)	2.88	(10)	0.76	g	0.84
155.	Thioanisole	0.76	4.39	(10)	2.39	(10)	2.00	g	2.22
156.	2,2'-Dichlorodiethyl sulfide	0.106	5.24	(7,21)	2.37	(5)	2.87	4.40[j]	2.06
157.	Methanol					(10,35)	3.72	3.83	3.89
158.	Methanethiol	760	1.39		0.48	(10)	0.91	0.94	1.02
159.	Ethanol					(10,35)	3.59	3.70	3.72
160.	Ethanethiol	527.3	1.55	(6c,21)	0.60	(2)	0.95	0.92	0.83[k]
161.	2,2,2-Trifluoroethanol					(29)	3.15	g	2.53[k]
162.	Ethylene glycol					(12b)	5.61	8.63[j]	8.02[k]
163.	1-Propanol					(12a,35)	3.56	3.55	3.54
	Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
164.	2-Propanol					(12a,35)	3.48	3.33	3.54
165.	Allyl alcohol					(35,34)	3.09	g	3.69[k]
166.	1,1,1-Trifluoro-2-propanol					(29)	3.05	l	2.35[k]
167.	2,2,3,3-Tetrafluoropropanol					(29)	3.59	l	1.96[k]
168.	2,2,3,3,3-Pentafluoropropanol					(29)	3.04	l	1.57[k]
169.	Hexafluoro-2-propanol					(29)	2.76	l	1.18[k]
170.	Glycerol					(12b)	6.15	13.20[j]	12.14[k]
171.	1-Butanol					(12a,35)	3.46	3.41	3.57
172.	2-Butanol					(12a,35)	3.38	3.19	3.37
173.	t-Butyl alcohol					(12a,35)	3.31	3.37	3.37
174.	2-Methyl-1-propanol					(12a)	3.31	3.33	3.37
175.	1-Pentanol					(12a)	3.89	3.28	3.19
176.	2-Pentanol					(12a)	3.22	3.04	3.19
177.	2-Methyl-1-butanol					(12a)	3.34	3.18	3.19
178.	2-Methyl-2-butanol					(12a)	3.28	3.23	3.19
179.	1-Hexanol	0.719	4.41	(12a,7,21)	1.21	(12a)	3.20	3.12	3.02
180.	3-Hexanol	4.88	3.58	(21,7)	0.80	(5)	2.70	2.90	3.02
181.	Cyclohexanol	1.66	4.06	(7,21)	0.42	(5)	3.63	3.84	3.87
182.	2,3-Dimethylbutanol	10.55	3.24	(7)	0.37	(5)	2.87	3.00	3.02
	Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
183.	2-Methyl-3-pentanol	5.13	3.55	(7)	0.70	(5)	2.85	2.82	3.02
184.	4-Methyl-2-pentanol	5.45	3.53	(7,21)	0.79	(5)	2.74	2.82	3.02
185.	2-Methyl-2-pentanol	7.87	3.37	(7,21)	0.49	(5)	2.88	3.08	3.02
186.	1-Heptanol	0.224	4.92	(12a,21)	1.80	(12a,5)	3.12	2.97	2.84
187.	1-Octanol	0.083	5.55	(12a,21)	2.34	(12a,5,35)	3.01	2.83	2.67
188.	Phenol					(20,10)	4.79	4.58	3.36
189.	4-Bromophenol					(20)	5.21	4.96[j]	3.78[k]
190.	4-Nitrophenol					(20)	7.77	6.45[j]	5.42[k]
191.	Thiophenol	1.92	3.99	(10)	2.12	(10)	1.87	g	1.65[k]
192.	2-Cresol					(20)	4.50	4.55	3.36[k]
193.	4-Cresol					(20)	4.49	4.55	3.36[k]
194.	4-Hydroxybenzaldehyde					(20)	7.66	7.85[j]	5.91[k]
195.	4-t-Butylphenol					(28)	4.34	4.28	2.82[k]
196.	Acetaldehyde					(11,35)	2.67	2.42	2.66
197.	Propanal					(11,35)	2.92	2.47	2.48
198.	Butanal					(11,35)	2.33	2.33	2.31
199.	Pentanal					(11)	2.22	2.18	2.17
200.	Hexanal					(11)	2.09	2.03	1.99
201.	Heptanal					(11)	1.91	1.89	1.79
202.	Octanal					(11)	1.68	1.74	1.61
203.	Nonanal					(11)	1.62	1.60	1.45

Table IV (Continued)

Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
204. trans-2-Butenal					(28,35)	3.10	3.12	3.13[k]
205. trans-2-Hexenal					(28)	2.70	2.75	2.77[k]
206. trans-2-Octenal					(28)	2.52	2.46	2.41[k]
207. trans,trans-2,4-Hexadienal					(28)	3.40	3.27	3.31[k]
208. Benzaldehyde	1.306	4.16	(20)	1.21	(9)	2.95	g	3.22[k]
209. Acetone					(11,35)	2.79	2.80	2.93
210. 2-Butanone					(11,35)	2.72	2.65	2.75
211. 2-Pentanone					(11)	2.58	2.51	2.58
212. 2-Heptanone					(11)	2.23	2.22	2.23
213. 2-Octanone					(11)	2.11	2.07	2.06
214. 2-Nonanone					(11)	1.82	1.93	1.88
215. 2-Undecanone					(11)	1.58	1.64	1.53
216. Acetophenone	0.372	4.70	(6a,7,21)	1.34	(2,14,17)	3.36	g	3.50
217. Acetic acid						4.91	4.92	4.94
218. Propionic acid						4.74	4.77	4.76
219. Butyric acid						4.66	4.62	4.58
220. Methyl formate					(18)	2.04	2.09	2.14
221. Ethyl formate	255.4	1.86	(7,21)	-0.08	(5)	1.94	1.96	1.98
222. Methyl acetate					(12b)	2.43	2.33	2.43
223. Propyl formate	85.8	2.33	(7,21)	0.51	(2,5)	1.82	1.81	1.81
224. Isopropyl formate	142.6	2.11	(7,21)	0.63	(2)	1.48	1.59	1.81
225. Ethyl acetate					(12b)	2.26	2.20	2.25
226. Methyl propionate	87.0	2.33	(7,21)	0.15	(2,5)	2.18	2.19	2.25
227. Isobutyl formate	43.3	2.68	(7,21)	1.00	(2)	1.63	1.58	1.63
228. Propyl acetate	33.0	2.75	(12b,21)	0.66	(12b,2,5)	2.09	2.05	2.08
229. Isopropyl acetate	61.1	2.48	(7,21)	0.54	(2,5)	1.94	1.83	2.08
230. Ethyl propionate	37.8	2.69	(7,21)	0.64	(2)	2.05	2.06	2.08
231. Methyl butyrate					(11)	2.08	2.04	2.08
232. Isoamyl formate	15.3	3.08	(7,21)	1.52	(2)	1.56	1.44	1.46
233. Butyl acetate	10.8	3.24	(7)	1.37	(2,5)	1.87	1.91	1.90
234. Isobutyl acetate	18.11	3.01	(7,21)	1.28	(2,5)	1.73	1.83	1.90
235. Propyl propionate	13.58	3.14	(7,21)	1.34	(2,5)	1.80	1.91	1.90
236. Isopropyl propionate	22.53	2.92	(7)	1.29	(2,5)	1.63	1.69	1.90
237. Ethyl butyrate	15.9	3.06	(7,21)	1.23	(2,5)	1.83	1.91	1.90
238. Methyl pentanoate					(11)	1.86	1.90	1.90
239. Amyl acetate	4.1	3.66	(7)	1.86	(2)	1.80	1.77	1.73
240. Isoamyl acetate	5.5	3.53	(7,21)	1.91	(2)	1.62	1.68	1.73
241. Propyl butyrate	4.8	3.59	(7,21)	1.92	(2,5)	1.67	1.76	1.73
242. Ethyl pentanoate	4.8	3.59	(7)	1.74	(2,5)	1.85	1.76	1.73
243. Methyl hexanoate					(11)	1.82	1.75	1.73
244. Hexyl acetate	3.02	3.71	(7)	2.05	(2)	1.66	1.62	1.55
245. Amyl propionate	3.6	3.72	(7)	2.25	(2)	1.46	1.62	1.55
246. Methyl octanoate					(11)	1.50	1.46	1.38
247. Ethyl heptanoate	0.86	4.43	(7)	2.74	(2,5)	1.69	1.47	1.38
248. Methyl benzoate	0.394	4.67	(6a,7)	1.53	(2)	3.14	g	3.00
249. Ethylamine					(12b)	3.38	3.46	3.53
250. Propylamine					(12b)	3.30	3.32	3.27
251. Butylamine					(12b)	3.21	3.17	3.17
252. Pentylamine					(27)	3.00	3.02	2.99
253. Hexylamine					(27)	2.96	2.88	2.81
254. Dimethylamine					(27)	3.14	3.14	3.38

Table IV (Continued)

Compound	P(mm)	-log c_g	Ref.	-log c_w	Ref.	Exptl	Group	Bond
255. Diethylamine					(27)	2.98	2.99	3.02
256. Pyrrolidine					(32)	4.01	3.93	3.28
257. Piperidine					(32)	3.74	3.78	3.10
258. Dipropylamine					(27)	2.68	2.70	2.66
259. Hexamethylenimine					(32)	3.60	3.64	2.92
260. Dibutylamine					(27)	2.43	2.41	2.30
261. Trimethylamine					(27)	2.37	2.29	3.06
262. Triethylamine					(27)	2.22	2.06	2.52
263. N-Methylpyrrolidine					(32)	2.91	3.08	2.96
264. N-Methylpiperidine					(32)	2.85	2.93	2.78
265. Ethylenediamine					(19)	7.15	8.15[j]	7.67
266. Acetonitrile					(10)	2.85	f	2.95
267. Propionitrile					(12b)	2.82	2.82	2.78
268. Butyronitrile					(12b)	2.67	2.67	2.61
269. Nitroethane	21.07	2.96	(7,21)	0.24	(2)	2.72	2.66	2.61
270. 1-Nitropropane	10.20	3.26	(7,21)	0.81	(2)	2.45	2.51	2.43
271. 2-Nitropropane	17.41	3.03	(7,21)	0.73	(2)	2.30	g	2.43
272. Nitrobenzene	0.284	4.82	(6a,7,21)	1.80	(2,5)	3.02	2.74	2.72
273. 2-Nitrotoluene	0.21[h]	4.95	(21,7)	2.32	(2)	2.63	2.72	2.73
274. 3-Nitrotoluene	0.20[h]	4.97	(21,7)	2.44	(2)	2.53	2.72	2.73
275. Pyridine					(13)	3.44	3.62	3.51
276. 2-Methylpyridine					(13)	3.39	3.48	3.52
277. 3-Methylpyridine					(13)	3.50	3.59	3.52
278. 4-Methylpyridine					(13)	3.61	3.59	3.52
279. 2-Ethylpyridine					(13)	3.17	3.29	3.35
280. 3-Ethylpyridine					(13)	3.37	3.40	3.35
281. 4-Ethylpyridine					(13)	3.46	3.40	3.35
282. 2,3-Dimethylpyridine					(13)	3.53	3.46	3.53
283. 2,4-Dimethylpyridine					(13)	3.56	3.46	3.53
284. 2,5-Dimethylpyridine					(13)	3.45	3.46	3.53
285. 2,6-Dimethylpyridine					(13)	3.37	3.35	3.53
286. 3,4-Dimethylpyridine					(13)	3.82	3.56	3.53
287. 3,5-Dimethylpyridine					(13)	3.55	3.56	3.53
288. 2-Methylpyrazine					(28)	4.04	4.16	4.34[k]
289. 2-Ethylpyrazine					(28)	4.00	3.97	4.16[k]
290. 2-Isobutylpyrazine					(28)	3.70	3.60	3.80[k]
291. 2-Ethyl-3-methoxy-pyrazine					(28)	3.22	i	4.31[k]
292. 2-Isobutyl-3-methoxy-pyrazine					(28)	2.70	i	3.95[k]

[a] Vapor pressure of pure solute (mm Hg) at 25°. [b] c_g is the concentration in the gas phase in moles per liter. [c] The first reference cited was used in calculations. [d] c_w is the water solubility (M). [e] $\gamma = c_s/c_w$, the activity coefficient referred to dilute aqueous solution. [f] Since this is the only possible compound that could contain the required group, its inclusion in the regression analysis would have been trivial. [g] Since this is one of a set of compounds whose log γ values were used to calculate a set of group contributions of the same size, the calculated value is identical to the experimental one. [h] Extrapolated from data at higher temperatures. [i] Data cited in other references differ significantly from this. [j] Omitted from the regression analysis because of a distant polar interaction. [k] Not included in the regression analysis. [l] This compound contained a group present only in compounds with distant polar interactions. Hence neither the interaction nor the group contribution could be calculated.

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Appendix

Table IV is arranged in the order: hydrocarbons, halohydrocarbons, ethers and sulfides, alcohols and mercaptans, phenols and thiophenols, aldehydes, ketones, carboxylic acids, esters, amines, nitriles, nitro compounds, pyridines, and pyrazines. The regression analyses were carried out using a computer program (BMDX 85).[16] In cases where there are no entries under P, log c_g, and log c_w, the values of log γ were obtained from data in the reference cited first.[1-15,17-35] In most cases the units had to be changed to obtain the values listed. Data on aldehydes in aqueous solution were not corrected to allow for the amount present as hydrate (1,1-diol). To permit a direct comparison of the correlating abilities of the group and bond contribution schemes, the latter was applied to the same 212 values of log γ that had been used for the group contribution correlation. The resulting standard deviation, 0.42, was essentially the same as that obtained in the bond correlation of 263 compounds that yielded the parameters in Table I and the calculated values of log γ in the last column of Table IV.

To help in assessing the quality of the correlations, a plot of log γ_{bond} *vs.* log γ_{exptl} is shown in Figure 1. The quality of the group contribution correlation may be inferred from the fact that the standard deviation was only 29% as large as that in the bond contribution correlation.

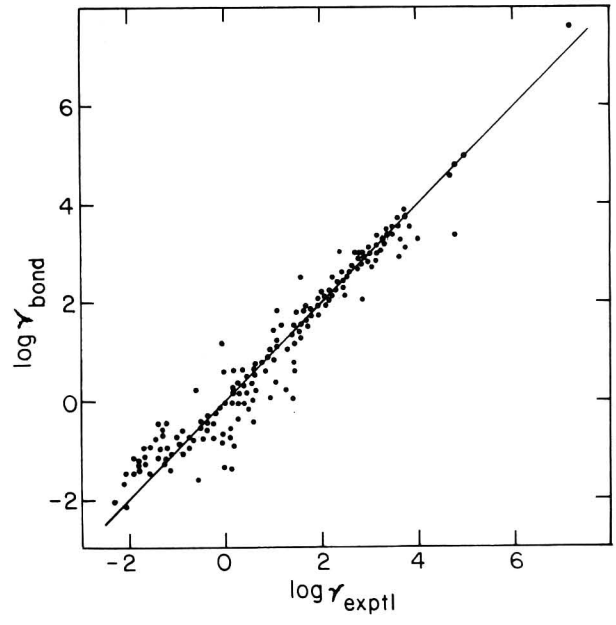

Figure 1. Plot of log γ_{bond} *vs.* log γ_{exptl}.

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Ranking Strong Acids *via* a Selectivity Parameter. I

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The relative facility of an acid in catalyzing the isomerization of methylpentanes to 2,2-dimethylbutane and *n*-hexane and the simultaneous deprotonation of carbonium ion intermediates is used to define a selectivity parameter, $k_{iso}/k_{ex} \equiv I/E$, characteristic of the medium. I/E is used to rank Lewis acids in HBr, HCl, HF, HSO_3F, and CF_3SO_3H. Data for two I/E scales, one for exchange with isopentane and the other for exchange with methylcyclopentane, are reported.

The choice of an acid catalyst for a hydrocarbon reaction is to a large extent governed by qualitative observations rather than quantitative information about existing possibilities. This situation exists because the relative acid strength of important acids is often unknown and because firm information about the stability of ionic intermediates in most acids is virtually unavailable.

To help clarify the issues recent work, notably that of Professor R. J. Gillespie and his colleagues, has aimed at determining Hammett acidity function values, H_0, for systems employing SbF_5 as a Lewis acid.[1-3] Using nitro aromatics as indicators, he has shown that some acids have about 10^8 times the protonating ability of 100% H_2SO_4. Acids in this range are generally useful for paraffin–olefin alkylation, paraffin isomerization, and certain types of cracking reactions. Using similar techniques we are in the process of extending Gillespie's measurements to other acids, but of added importance, we have developed a new procedure to classify acids according to the manner in which they stabilize or interact with alkyl carbonium ions.

Our procedure is aimed at giving us quantitative information about the nucleophilicity of a given acid solution. Specifically it tells us if an alkyl cation can rearrange with or without deprotonating during its lifetime in the acid. It should be noted that the nucleophilicity of an acid system is not necessarily directly related to its acidity as a Brønsted acid, a property more properly evaluated by an H_0 type measurement.

This information is acquired by simultaneously reacting a hydrocarbon which contains an essentially uniform distribution of tritium around its skeleton with another molecular weight but unlabeled hydrocarbon over any acid catalyst. A "perfect" acid will allow all isomerizations to occur without hydrogen exchange while a "poor" acid, which is unable to stabilize the ion, will tend to induce faster exchange than isomerization. The ratio of isomerization to exchange rate constants, k_{iso}/k_{ex} or I/E, is defined as a selectivity parameter which permits the ranking of all strong acids. This parameter should be useful until alternate exchange mechanisms become important. At very high acidities direct protonation and displacement may become significant but it is not a serious factor through 2 M SbF_5–HSO_3F solutions which have H_0 values > -18.

Strategical Approach to the Problem

In order to obtain the selectivity parameter, it is first necessary to prepare a suitably labeled hydrocarbon. This was done by contacting 2- or 3-methylpentane with 98% H_2SO_4 containing tracer quantities of T_2O (1 mCi/ml) for several days. In this acid, the methylpentanes isomerize without undergoing chain branching rearrangements and exchange all protons except the tertiary hydrogen.[4-13] The labeled methylpentanes were diluted with unlabeled methylpentanes and mixed with isopentane (mixture 1) or methylcyclopentane (mixture 2).

Since it is known that during the isomerization of methylpentanes to an equilibrium mixture of all isomers there is a rapid equilibration of 2-methylpentane, 3-methylpentane, and 2,3-dimethylbutane which is followed by a slower conversion of this mixture to 2,2-dimethylbutane and *n*-hexane[4,14,15] we choose the rate of the latter process, k_{iso}, as a measure of the isomerization activity of the acid.

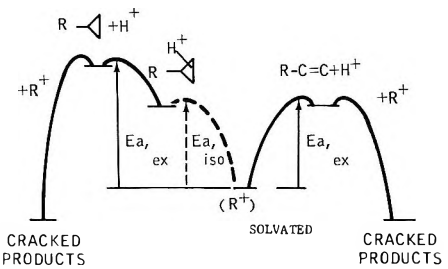
We also measure the rate of depletion of radioactivity in the total hexane fraction. The isomerization and overall exchange processes are both assumed to follow first-order kinetics and the rate constants are obtained from log concentration or radioactivity *vs.* time plots. In the more reactive acid systems there is substantial uncertainty in the rate

constants because they are based on only one or two data points at high conversion levels.

All reactions were initiated with a small but constant amount of *tert*-butyl chloride. Some systems were unable to rapidly attain a steady-state ion concentration and for these the rate constants are crudely estimated from initial conversion data only. For most of the systems studied, however, an error of less than ±10% of the reported rate constants is estimated.

The ratio, k_{iso}/k_{ex}, is the selectivity parameter. A perfect acid would exhibit a ratio of ∞ while a "poor" acid would have a value of zero. Before proceeding further, it is appropriate to consider a general reaction coordinate diagram for the possible isomerization, exchange, and cracking reactions the ions are likely to undergo (Scheme I).

Scheme I
General Scheme Leading to Isomerization, Exchange, and Cracking *via* Olefins or Alkycyclopropanes



Hexane isomerization can take place with or without H^+ exchange, exchange being more prevalent in more nucleophilic media. Exchange occurs through alkenes or alkylcyclopropane intermediates.[25] A potentially bothersome side reaction is cracking which involves a bimolecular reaction of the same intermediates and carbonium ions.[16,17] It is possible to exchange without cracking if the concentrations of ions and intermediates are both low.

It is important to note that the relative isomerization and exchange rates are both assumed to go through a common carbonium ion intermediate. The ratio k_{iso}/k_{ex} is assumed to reflect the properties of the medium and should be independent of physical factors like stirring rates and the heterogeneity of the system.

These considerations apply to the major paths for isomerization and exchange and are consistent with many studies in H_2SO_4.[4-13] Exchange by other routes has been considered but are believed to make only a minor contribution to the data. One alternate path involves the isomerization of a tertiary tritiated ion to a secondary ion, hydride abstraction to this site, and then detritiation by hydride transfer from the tertiary position. A second involves direct proton displacement reactions on the paraffins.

The first path is believed to be of little importance because it depends on a bimolecular reaction involving an extremely low concentration of secondary ions. The second path would require an increase in exchange rate with acid strength but with the possible exception of some concentrated SbF_5 solutions there is little reason to support this mechanism in the acidity range being studied.

We arbitrarily use k_{iso}/k_{ex} as the selectivity parameter. It might be better to use $k_{iso}/(k_{ex} + k_{crack})$, but the selected ratio ought to be a fair indicator of acid character, especially where side reactions are minimized and we choose to handle our data in this way.

Experimental Conditions

Reactions have been carried out between −93 and +23°. Approximately equal volumes of the hydrocarbons and acids were used and isomerization and exchange were followed by periodically withdrawing samples for analysis on a radioassaying gas chromatograph system. In every run the reaction was initiated with a small amount of *tert*-butyl chloride which was predissolved in the hydrocarbons. The concentration of *tert*-butyl chloride in the acid was 0.12 *M*. When using liquid HBr or HCl a series of experiments of varying duration was made, each run providing one point for the kinetic analyses.

Reaction was conducted in a series of small Hastelloy C vessels which were compatible with the acids studied. The acids characterized in this program are $AlBr_3$–HBr, $AlCl_3$–HCl, HF, SbF_5–HF, TaF_5–HF, NbF_5–HF, HSO_3F, SbF_5–HSO_3F, TaF_5–HSO_3F, NbF_5–HSO_3F, CF_3SO_3H, SbF_5–CF_3SO_3H, TaF_5–CF_3SO_3H, and NbF_5–CF_3SO_3H.

Measurements were made at several molar concentrations of the Lewis acid. The range was normally 0.5–2.0 although 5 *M* SbF_5–HF solutions were also studied. The Lewis acids, $AlBr_3$ and SbF_5, were distilled in glass equipment before use. Aluminum chloride was sublimed in an N_2 atmosphere and TaF_5 and NbF_5 were utilized as received from the Ozark-Mahoning Co. Anhydrous HBr and HCl (Matheson) were used as received. Hydrogen fluoride was distilled in an all steel apparatus and HSO_3F was distilled in glassware. Trifluoromethanesulfonic acid was distilled in glassware and conductivity measurements indicated it had 2 mol % water. As indicated in the text there is some uncertainty about the stability of CF_3SO_3H and the solutions containing Lewis acids.

Table I
Low-Temperature Isomerization in Acid Systems i-C_5H_{12} + 3-$CH_3C_5H_{11}$*

Acid	T, °C	k_{iso}, hr^{-1} [a]
0.5 *M* SbF_5–HSO_3F	−78	0.02
2 *M* SbF_5–HSO_3F	−78	0.02
0.5 *M* TaF_5–HSO_3F	−78	0.03
2 *M* TaF_5–HSO_3F	−78	0.04
0.5 *M* NbF_5–HSO_3F	−78	0.03
2 *M* NbF_5–HSO_3F	−78	0.03
0.5 *M* $AlBr_3$–HBr	−78	0.02
2 *M* $AlBr_3$–HBr	−78	0
0.5 *M* $AlCl_3$–HBr	−93	0

[a] Isomerizations are of type A only.

Results and Discussion

It has been indicated that when 3-methylpentane isomerizes there are some rearrangements which occur relatively easily and others which occur more slowly. For this work we distinguish between the reactions which lead to the relatively rapid equilibration of 2-methylpentane, 3-methylpentane, and 2,3-dimethylbutane, which will be called type A isomerizations, and the isomerization of this mixture of isomers to *n*-hexane and 2,2-dimethylbutane, type B. Type B isomerization rates are used in the selectivity parameter, k_{iso}/k_{ex}.

type of isomerization: definitions

$$2\text{-}MC_5 \rightleftharpoons 3\text{-}MC_5 \rightleftharpoons 2,3\text{-}DMC_4 \qquad \text{A}$$

$$2\text{-}MC_5 + 3\text{-}MC_5 + 2,3\text{-}DMC_4 \xrightarrow{S} n\text{-}C_6 + 2,2\text{-}DMC_4 \qquad \text{B}$$

Type A isomerizations at low rates were found in all HCl, HBr, and HSO_3F systems at −78 or −93° (see Table I). Type B isomerizations, however, were negligible and the exchange rates were also relatively slow. These experiments provide base case or background information for higher temperature studies but are not used in further assessing the acid solutions.

The same systems and additional ones based on HF and CF_3SO_3H have been studied at ambient conditions. Both the isomerization and exchange rates are listed in Table II, and an example of the approach to isomerization and exchange equilibrium in 2 *M* SbF_5–HSO_3F is shown in Figure 1. Both reactions reached equilibrium in less than 2 hr. At

Table II
Isomerization and Exchange in Acid Systems, 23°
i*-C_5H_{12} + (3-$CH_3C_5H_{11}$)

Acid	"B" k_{iso}, hr^{-1}	k_{ex}, hr^{-1}	*I*/*E*
0.7 *M* $AlBr_3$–HBr	>1.1	0.25	>4.3
2 *M* $AlBr_3$–HBr	>>0.6	0.02	>35/1
1.9 *M* $AlCl_3$–HCl	>0.8	0.25	>3.3
1.6 *M* $AlCl_3$–HCl	>1.6	0.24	>6.6
0.45 *M* $AlCl_3$–HCl	1.1	0.74	1.5
0.37 *M* $AlCl_3$–HCl	0	0.26	0
HF	0	0.03	0
0.5 *M* SbF_5–HF	1.76	0.68	2.6
2 *M* SbF_5–HF	2.42	0.69	3.5
5 *M* SbF_5–HF	2.98	1.84	1.6
0.5 *M* TaF_5–HF	0.76	0.56	1.35
2.0 *M* TaF_5–HF	0.58	0.07	8.29
0.5 *M* NbF_5–HF	1.37	2.52	0.54
HSO_3F	1.42	>3.34	0.42
2 *M* SbF_5–HSO_3F	1.42	0.79	1.80
2 *M* TaF_5–HSO_3F	0.72	0.62	1.16
CF_3SO_3H	0	>5.92	0
2 *M* SbF_5–CF_3SO_3H	2.68	0.62	4.25
2 *M* TaF_5–CF_3SO_3H[a]	4.89	4.76	1.03
2 *M* NbF_5–CF_3SO_3H[a]	2.59	>4.49	<0.58

[a] Unidentified products formed in this acid.

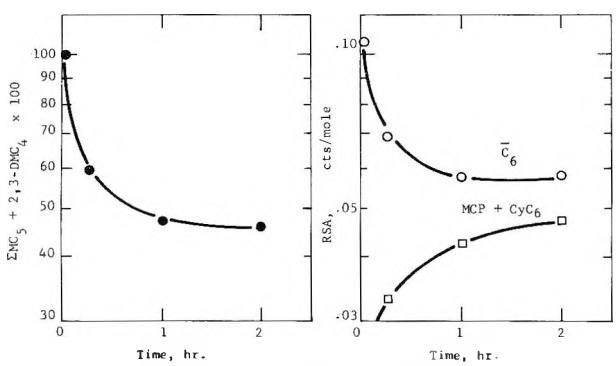


Figure 1. Isomerization and exchange equilibrium reached rapidly in 2 *M* SbF_5–HSO_3F. RSA or relative specific activity is a measure of the radioactivity of the sample.

this time the average C_6 molecule had a relative specific activity (RSA) of 0.057 counts/molecule while an average naphthene, methylcyclopentane or cyclohexane, had an RSA of 0.047. If we assume that there are 13 exchangeable protons in C_6H_{14} and 11 exchangeable protons in the alicyclic compounds, we find the average counts per proton to be nearly identical in both sets of molecules, (0.00438 count/H)C_6H_{14} and (0.00427 count/H)C_6H_{12}. Thus, all exchangeable protons have been equilibrated.

The data indicate a wide range in behavior of the acid systems varying from 2 *M* $AlBr_3$ in HBr in which ions isomerize more readily than they exchange to HF and CF_3SO_3H in which exchange is faster. It might be noted that our estimate of k_{iso} for 2*M* $AlBr_3$–HBr is very low because the system was at equilibrium at the time of sampling. Nevertheless, little detritiation of the hexanes had occurred in this time or in more prolonged experiments.

The data in Table II can be regrouped to compare the selectivity parameter, *I*/*E*, when SbF_5, TaF_5, and NbF_5 are added to HF, HSO_3F, and CF_3SO_3H (see Table III). When this is done, we find that SbF_5, TaF_5, and NbF_5 lead to the same ordering of 0.5 *M* solutions in HF and 2 *M* solutions in HSO_3F and CF_3SO_3H. In all of these, isomerization with solutions containing SbF_5 proceed with less exchange than

Table III
Selectivity Parameter, *I*/*E*

	HF[a]	HF[b]	HSO_3F[b]	CF_3SO_3H[b]
SbF_5	2.6	3.5	1.8	4.3
TaF_5	1.4	8.3	1.2	1.0
NbF_5	0.5			<0.5
None	0	0	0.4	0

[a] 0.5 *M* MX_n. [b] 2.0 *M* MX_n.

Table IV
Isomerization and Exchange in HSO_3F, 23°
MCP + (3-Methylpentane)*

Lewis acid, *M*	k_{iso}	k_{ex}	*I*/*E*
SbF_5, 2	2.0	1.6	1.2
TaF_5, 2	0.8	0.9	0.9
NbF_5, 2	0.7	1.0	0.7

occurs with TaF_5 and NbF_5. The ordering of the acids is apparently proportional to the acidity of the systems as measured on the H_0 scale,[18-20] which indicates that SbF_5–HF is about 2 units more acidic than TaF_5–HF which in turn is slightly more acidic than NbF_5–HF.

The 0.5 *M* solutions of TaF_5–HF are nearly saturated and ought to reflect a maximum acidity at ambient conditions. Hence it is extremely interesting to find that the selectivity parameter increases when an excess of TaF_5 is added. It is known that TaF_5 dissolves in HF far beyond its solubility limit when the acids are mixed in the presence of hydrocarbons. This indicates that some complex of TaF_5 and organic matter, probably a soluble carbonium ion–TaF_6 salt, is formed. The presence of this material evidently serves the useful purpose of mainly deaccelerating the exchange reaction and the system behaves as though it were more acidic and less nucleophilic.

Why this is so is a matter of speculation. A plausible reason for the small effect on isomerization is that the soluble salt exerts a common ion effect on the alkyl cation concentration, *i.e.*, reduces it. This would be consistent with the apparent drop in k_{iso} from 0.76 to 0.58 hr^{-1} in proceeding from 0.5 to 2.0 *M* TaF_5–HF. Not easily understandable, however, is the larger drop in the rate of exchange. One might have expected that an increased concentration of TaF_6^- would augment the exchange and further studies of this phenomenon are planned.

The Selectivity Parameter Is Compressed by Methylcyclopentane. The preceding data were obtained with mixture I. In Table IV are shown comparable data obtained with mixture II where methylcyclopentane, MCP, is used in place of isopentane. It was expected that MCP would function as a cracking inhibitor and prevent cracking reactions which make it difficult to interpret some of the kinetic information in the prior experiments. MCP did suppress cracking but surprisingly led to generally faster isomerization and exchange rates than were found when isopentane was used. The *I*/*E* ratios lie in the same order as before but the ratio is reduced markedly. The reduction stems from the relatively more rapid increase in the rate of exchange.

The selectivity parameters obtained with both hydrocarbons are compared in Table V. It might be expected that using MCP will lead to an increase in the total concentration of ions dissolved in the acid because the methylcyclopentyl ion normally appears to be more stable than any of the alkyl ions.[21-23] If this is so, there might be a concomitant increase in isomerization rates, in counterion and ole-

Table V
Selectivity Parameter Is Affected by the Hydrocarbon

Hydrocarbon	2 *M* SbF_5–HSO_3F	2 *M* TaF_5–HSO_3F
Isopentane	1.8	1.2
Methylcyclopentane	1.2	0.9

Table VI
Selectivity Parameter of 2 *M* Acid Solutions[a]

Acid	*I*/*E*
$AlBr_3$–HBr	>35
TaF_5–HF	8.3
$AlCl_3$–HCl	8 est.
SbF_5–CF_3SO_3H	4.3
SbF_5–HF	(3.5)
SbF_5–HSO_3F	1.8
TaF_5–HSO_3F	1.1
TaF_5–CF_3SO_3H	1.0
NbF_5–CF_3SO_3H	0.6

[a] Obtained with the *i*-C_5H_{12}–3-MC_5* mixture.

Table VII
Selectivities of 0.5 *M* Acid Solutions[a]

Acid	*I*/*E*
(0.7) $AlBr_3$–HBr	4.3
SbF_5–HF	2.6
$AlCl_3$–HCl	1.5
TaF_5–HF	1.4
NbF_5–HF	0.5

[a] Obtained with the *i*-C_5H_{12}–3-MC_5* mixture.

fin concentrations, and a reduction in acidity of the solution. The latter effects would tend to accelerate exchange. Thus, both isomerization and exchange rates should increase upon raising the ionic strength and this is seen in the data. For example, the isomerization rate constant in 2 *M* SbF_5–HSO_3F increased from 1.41 to 2.00 hr^{-1} when isopentane was replaced with MCP. Offsetting increases in the exchange rate led to the compression in Table V.

Ranking the Acids. In Table VI, the selectivity parameter for 2 *M* solutions of the acids listed in Table II is tabulated. The ordering indicates that $AlBr_3$–HBr provides the best ion stabilizing medium. As there is no simple relationship between this composite property and proton activity one cannot say that $AlBr_3$–HBr is also the strongest Brønsted acid. In Table VII a shorter comparison of 0.5 *M* solutions is shown.

Although both of the comparisons indicate that $AlBr_3$–HBr provides the most stabilizing acid, the data in these tables should be used with care. Reasons for caution are that some of the systems are heterogeneous and there are large differences in solution properties of the Brønsted acids. In some cases the data may be biased by cracking or the fact that some of the acids may be inherently unstable.

These problems clearly exist for $AlCl_3$–HCl where sight glass studies indicate there is virtually no solubility of $AlCl_3$ in HCl[24] and its concentration in hydrocarbons is likewise known to be low. This system is certainly heterogeneous and if reaction occurs in different phases it might affect the selectivity parameter. Similarly CF_3SO_3H–MX_n systems may rate highly but the prolonged stability of

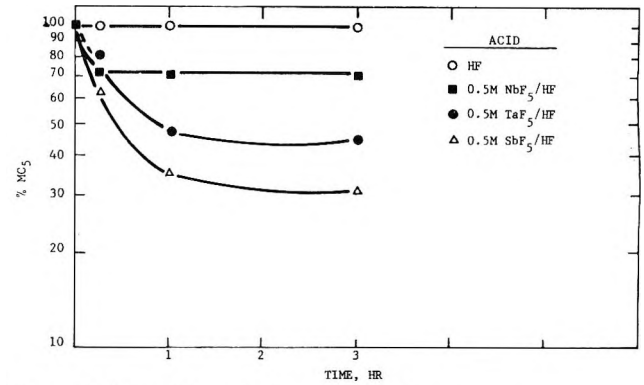


Figure 2. *I*/*E* and long-lived ions go together.

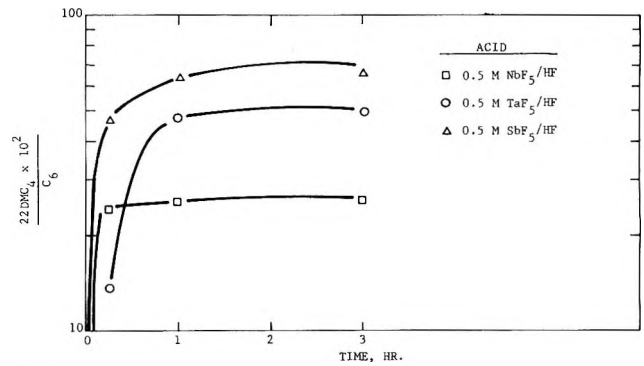


Figure 3. Equilibrium 2,2-DMC_4 not obtained with NbF_5–HF.

CF_3SO_3H is uncertain. In particular, during isomerization with TaF_5–CF_3SO_3H a number of low molecular weight and unidentified products were produced and conclusions on these systems are tentative.

Another concern is that cracking reactions occurred to varying degrees with $AlBr_3$–HBr, $AlCl_3$–HCl, SbF_5–HF, TaF_5–HF, and NbF_5–HF during the reactions of isopentane and 3-methylpentane. Cracking was severely reduced in later work with methylcyclopentane, and the trends established with isopentane have been generally repeated but full comparisons are not yet available.

In spite of these problems an indication that the selectivity parameter provides more than a qualitative comparison of the acids may be obtained by examining the apparent catalyst life of the 0.5 *M* solutions of SbF_5, TaF_5, and NbF_5 in HF (see Figure 2). These acids had selectivity parameters of 2.6, 1.4, and 0.5 and both the SbF_5 and TaF_5 solutions had sufficient catalyst life to allow isomerization to approach equilibrium. (With SbF_5 the product distribution is slightly distorted because of cracking which tends to selectively remove the reactive components leaving an excess of 2,2-dimethylbutane and *n*-hexane.)

Of more significance, however, is the observation that in the NbF_5 solution, rapid initial isomerization was followed by nearly immediate cessation, the reaction stopping with 25% 2,2-dimethylbutane in the product whereas about 50% should be present at equilibrium. In HF alone, there is essentially no formation of 2,2-dimethylbutane under comparable conditions; see Figure 3.

These results may be taken to mean that following solvolysis of the initiator, *t*-C_4H_9Cl, one generates an alkyl ion with increasing stability in the acids: HF < NbF_5–HF < (TaF_5–HF, SbF_5–HF). In HF, perhaps because its acidity is lower than the other acids, the initial butyl ion concentration appears to be immediately lowered and whatever C_6 ions form do not have sufficient "freedom" or reactivity to undergo the skeletal rearrangement to a 2,2-dimethylbutyl ion. In NbF_5–HF, the C_6 ions first formed do undergo this

rearrangement, but a side reaction which evidently destroys the active isomerizing intermediate must occur simultaneously because of the severe change. In TaF_5–HF and SbF_5–HF the stability of the intermediates is evidently prolonged because of the relatively smoother and continual isomerization to equilibrium which is found.

Thus, there is a clear distinction between Lewis acids in HF which have a high selectivity parameter and allow isomerization to 2,2-dimethylbutane and those with low values where the catalyst becomes deactivated. If the comparison can legitimately be made between different acids, HF, HSO_3F, CF_3SO_3H, HCl, and HBr, the selectivity parameter may provide the first consistent scale for a quantitative comparison between the strong acids. As such, it should complement acidity function studies (H_0) currently being carried out in these and other laboratories on the strong acid systems. At this time the ordering in Tables VI and VII is unique in providing the first comparison of $AlBr_3$–HBr, $AlCl_3$–HCl, the older strong acid systems, and a variety of other acids which are of current interest as "superacids," "magic" acids, and generally strong acid media.

Registry No.—$AlBr_3$, 7727-15-3; HBr, 10035-10-6; $AlCl_3$, 7446-70-0; HCl, 7647-01-0; HF, 7664-39-3; SbF_5, 7783-70-2; TaF_5, 7783-71-3; NbF_5, 7783-68-8; HSO_3F, 7789-21-1; CF_3SO_3H, 1493-13-6; isopentane, 78-78-4; methylcyclopentane, 96-37-7.

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(24) Unpublished results of H. Solomon and G. M. Kramer. Hydrogen chloride was liquefied at ambient conditions in a Jerguson gauge containing several grams of $AlCl_3$. No visible change in the $AlCl_3$ occurred. The gauge was equipped with a magnetically driven stirrer from an Autoclave Engineers 300-ml Autoclave and surrounded by an oil bath which could be heated. The system could be observed to undergo critical opalescence at about the critical point of pure HCl, 51°, indicating that little $AlCl_3$ is in solution.
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Ranking Strong Acids *via* the Selectivity Parameter. II

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Selectivity parameter measurements of 2 *M* mixtures of Lewis acids in Brønsted acids are reported. Overlapping comparisons of inorganic bromides and fluorides in HBr rank the acids as $AlBr_3 > GaBr_3 > TaF_5 > BBr_3 > BF_3$, TiF_4, HfF_4. Lewis acids are found to exhibit their acidity more easily in HF than in HBr. Two scales, $(I/E)_{i\text{-}C_5}$ and $(I/E)_{MCP}$, are found to correlate with one another. They also relate to H_0 measurements within a given Brønsted acid but H_0 values with different Brønsted acids do not permit an estimate of the ion stabilizing properties of the system.

It has recently been proposed that strong acids can be characterized by their ability to stabilize carbonium ions.[1] The ratio of two reactions of methylpentanes, namely the rate of isomerization to 2,2-dimethylbutane and *n*-hexane divided by the rate of exchange of protons with isopentane or methylcyclopentane, is defined as the selectivity parameter, $(I/E)_{i\text{-}C_5}$ or $(I/E)_{MCP}$, which measures the ion stabilizing capacity of the acid.

The I/E ratio is an empirical kinetic parameter offering insight into the overall or inherent ability of an acid to permit the rearrangement of ions with a minimum of proton transfer from the ion or a protonated alkylcyclopropane intermediate to the acid. It does not measure the position of an ion $\rightleftharpoons$ olefin + H^+ or H^+–R-cyclopropane $\rightleftharpoons$ H^+ + R-cyclopropane equilibrium, but one would expect that these shift increasingly to the left as I/E increases.

The initial work provided I/E values for $AlBr_3$–HBr, $AlCl_3$–HCl, and SbF_5, TaF_5, and NbF_5 in HF, CF_3SO_3H, and HSO_3F. Although this permits an immediate ranking of the acid systems with respect to ion stability it is not clear if it provides a real comparison of the acid strength of the Lewis acids since different Brønsted acids were used as solvents. Thus, while $AlBr_3$–HBr has a larger I/E than SbF_5–HF or SbF_5–HSO_3F, one may ask if this reflects the fact that $AlBr_3$ is a stronger acid than SbF_5 or if HBr is a less nucleophilic solvent which provides a better medium than HF or HSO_3F. One means of answering this is to determine I/E with the same Lewis acids in both HBr and HF or other solvents. Thus, one of the objectives of the current work was to obtain overlapping comparisons of the selectivity parameter and hence the relative strength of Lewis acids in HBr and HF. Another objective was to evaluate a wider range of systems than previously studied and a third objective was to compare the $(I/E)_{i\text{-}C_5}$ and $(I/E)_{MCP}$ scales more closely. Finally, it was hoped that the I/E scales could be related to H_0 (Hammett acidity function) measurements which should provide a measure of proton activity where such data are available.

Table I
Selectivity Parameter in 2 *M* Acid Mixtures

Acid	C_5 + 3-MC_5*				MCP + 3-MC_5*			
	k_{iso}, hr^{-1}	k_{ex}, hr^{-1}	I/E	$(k_{iso})_A$, hr^{-1}	k_{iso}, hr^{-1}	k_{ex}, hr^{-1}	I/E	$(k_{iso})_A$, hr^{-1}
				Solvent: HBr				
$AlBr_3$	≫0.6	0.02	>35	vf	>2.46	0.65	>3.8	vf
$GaBr_3$	>2.7	1.05	>2.6	>3	0.39	0.44	0.9	>4
TaF_5	0.028	0.16	0.17	~3.7	0.024[a]	0.21	0.11[a]	1.9
BBr_3	0	?	0	0.26	0.0015[a]	0.31	0.005[a]	0.12
TiF_4					0	0.32	0	0
BF_3					0	0.16	0	0
HfF_4					0	0.06	0	0
				Solvent: HF				
TaF_5	0.58	0.07	8.29	vf	0.72	0.34	2.1	vf
					0.55	0.20	2.8	vf
SbF_5	2.42	0.69	3.5	vf	>2.84	1.89	>1.50	vf
					>2.59	1.75	>1.48	vf
BF_3	>5.50	>4.24	1.30	vf	(0.004)	0.35	0.01	2.1
					0.026[a]		0.07[a]	
TiF_4	>0.035[a]	0.96	0.036[a]	>2.8	0.001[a]	0.49	0.002[a]	0.08
HfF_4	0.035[a]	2.76	0.013[a]	2.8	0.0006[a]	0.69	0.0009[a]	0.05
				Solvent: HCl				
$GaCl_3$					1.39	0.25	5.6	>5.2
$AlCl_3$			8 (est)		0.47	0.32	1.5	
BCl_3					0	0.16	0	0

[a] Estimated by assuming $k_{iso} = \frac{1}{80}(k_{iso})_A$, as reported in $AlCl_3$–HCl at 100° (B. L. Evering and R. C. Waugh, *Ind. Eng. Chem.*, **43**, 1820 (1951)). vf, very fast.

Experimental Section

The experimental conditions were slightly different from those previously reported.[1] The current reactions were carried out in 10- or 45-ml Hastelloy C reactors with about 1:3 hydrocarbon to acid volume ratios. Two molar mixtures or solutions of Lewis acids in hydrogen halides were prepared on the assumption of ideal behavior of the components. Sufficient hydrogen halide was used to ensure the presence of a liquid HX phase in all experiments. As before, a 0.12 *M* solution of *tert*-butyl chloride in the hydrocarbon was used to initiate the reactions.

Commercially available BCl_3, BBr_3, BF_3, TiF_4, HfF_4, $GaCl_3$, and $GaBr_3$ without further purification as well as the TaF_5 and SbF_5 previously employed were used in this work. Selectivity parameters were obtained in HBr, HF, and HCl. Most of the reactions were run with both isopentane and methylcyclopentane.

Results

A composite of the selectivity parameters obtained in 2 *M* solutions or mixtures of Lewis acids in HBr, HF, and HCl in this and prior work is reported in Table I. The table lists k_{iso}, the rate constant for the conversion of an equilibrium mixture of 2-MC_5, 3-MC_5 and 2,3-DMC_4 to 2,2-DMC_4 and *n*-C_6; k_{ex}, the constant for proton exchange between the tritium labeled C_6 reactants and unlabeled *i*-C_5 or MCP; I/E which is k_{iso}/k_{ex}; and $(k_{iso})_A$, the rate constant for the conversion of 3-MC_5 to 2-MC_5.

Because of the range of activity of the systems studied, all of these parameters have been utilized in ranking and characterizing the acids.

Discussion

(A) Relative Strength of Lewis Acids. In HBr. The relative strengths of many strong Lewis acids are unknown although various orders have been proposed. A good review of the extent and limitations of acidity estimtes is provided by Satchell and Satchell[2] and a summary of information on the metal fluorides has been made by Haartz and McDaniel.[3] The I/E scale may permit a more extensive comparison but until now has not allowed a direct comparison of fluorides with other halides because of differences in the solvent.

To avoid this problem, HBr was chosen as the common solvent for investigating a series of metal bromides and fluorides. HBr was picked because thermodynamic considerations suggested that metal fluorides would be stable and not undergo fluoride–bromide exchange. This is primarily because metal–fluoride bonds are stronger than metal–bromide bonds. Metal chlorides were not studied in HBr because in many instances they are known to rapidly exchange. It should be noted that HF could not be used as a common solvent for the bromides because of the immediate formation of metal fluorides.

The Lewis acids studied include $GaBr_3$, BBr_3, TaF_5, HfF_4, BF_3, and TiF_4 in addition to $AlBr_3$ which was investigated earlier. Experiments were also attempted with SbF_5 but mixing was extremely poor owing to its apparent insolubility in HBr and its high viscosity, so that no meaningful results were obtained. The solubility of the Lewis acids in HBr was not determined so that the I/E characterization of the formal 2 *M* "solutions" is very possibly that of saturated solutions in the majority of cases. Solubility determinations would be extremely valuable but would require considerably different equipment than was available for this work. In any case, the systems reported were all well mixed.

The relative acidity of the Lewis acids in HBr lies in the order $AlBr_3 > GaBr_3 > TaF_5 > BBr_3 > (TiF_4, BF_3, HfF_4)$. This order is deduced by sequentially using the data in Table I as criteria. First, we use the $(I/E)_{MCP}$ and $(I/E)_{i\text{-}C_5}$ ratios. Next we utilize k_{iso} which is the rate constant of the slowest rearrangement, and then we turn to $(k_{iso})_A$, the rate constant for the facile isomerization of 3-MC_5 to 2-MC_5.

This clearly orders the acids from $AlBr_3$ to TiF_4. The error in determining any of the rate constants increases with the rapidity of reaction and is estimated at less than ±10% where k is between 2 and 0.05 hr^{-1}. It becomes very

Table II
Ion Stability Is Proportional to Acid Strength in HBr

	$(k_{iso})_{MCP}$	Rel [R⁺]	k_{ex}	$[Ex/R^+]_{norm}$
$AlBr_3$	>2.46	1	0.65	1
$GaBr_3$	0.39	0.16	0.44	4.2
TaF_5	0.024	0.010	0.21	32.0
BBr_3	0.0015	0.0006	0.31	794.0

large with faster reactions and little quantitative significance should be placed on such values. In considering the $AlBr_3$ data in i-C_5, the k_{iso} value is certain to be much larger than 0.6 and $(I/E)_{i\text{-}C_5}$ much larger than 35, the problem being that the shortest interval used to estimate the kinetics was twice as long as in the other experiments and the conversion too high to permit a more useful determination. The $AlBr_3$ data in MCP offer a much better idea of its acidity relative to the other acids.

The isomerization rate constants should reflect the steady-state ion concentrations developed in the MX_n–HB_r solutions:

$$R^+ \rightleftharpoons H^+ + R^= \quad (1)$$

or

$$R^+ \rightleftharpoons H^+ + R\text{—}\triangleleft \quad (2)$$

$$HBr + MX_n \overset{K_1}{\rightleftharpoons} \underbrace{H^+ \cdot MX_nBr^-}_{B} \overset{K_2}{\rightleftharpoons} \underbrace{H^+ \| MX_nBr^-}_{C} \quad (3)$$

The ions should be in equilibrium with olefins or alkylcyclopropanes with the proton activity being governed by the equilibria of eq 3. Presumably, the solvated proton may exist in either a tight ion pair, B, or solvent separated ion pair, C, no distinction being made in this work. The concentration of *B and C* ought to measure the Brønsted acidity of HBr–MX_n but since K_2 may be a function of the anion as well as of the solvent, and B and C may react at different rates, it seems unwarranted to take the relative isomerization rates as more than a qualitative indication of acidity. Nevertheless, it is interesting to analyze the isomerization and exchange data to search for inherent changes in ion stability with acid strength. This may be done by assuming the isomerization rates are proportional to the total ion concentration in HBr and normalizing the data in Table I, to obtain the relative concentration of ions formed with the various Lewis acids. From these values and the measured exchange rates the relative rates of exchange or deprotonation per ion can be calculated. These values are given in the last column of Table II and when they are compared with the ion concentrations in column 3 it is clear that ion stability is proportional to the total ion concentration or the acid strength.

The ordering of TiF_4, BF_3, and HfF_4 is less certain than the other Lewis acids in HBr. One might attempt to place these in accord with the decreasing exchange rate but as acidity decreases one expects two opposing factors to become important. These are that the ion concentration should decrease as acidity drops, suggesting a lower exchange rate, but the basicity of the medium simultaneously increases and this should augment the exchange. It is difficult to decide which is most significant and hence ordering solely on the HBr exchange data is unreliable.

(B) Relative Strength in HF. Consideration of the HF solutions enables one to order the metal fluorides. Again, some of the mixtures are heterogeneous while others may be homogeneous. The 2 *M* mixture of TaF_5 far exceeds its solubility which is *ca.* 0.5 *M* but the 2 *M* SbF_5 solution

Table III
Apparent Acidity Deduced from Ion Stabilizing Ability of Lewis Acids in HBr and HF[a]

HBr	$(I/E)_{MCP}$	HF	$(I/E)_{MCP}$
$AlBr_3$	>3.8		
$GaBr_3$	0.9		
TaF_5	0.11	TaF_5	2.1–2.8
BBr_3	0.0005	SbF_5	>1.5?
BF_3, TiF_4, HfF_4		BF_3	(0.01–0.07)
		TiF_4	0.002
		HfF_4	0.0009

[a] 2 *M* mixtures or solutions.

should be homogeneous. As noted previously, the presence of excess TaF_5 led to a reversal of the ion stabilizing capability of SbF_5 and TaF_5 which was deduced from I/E values on more dilute and fully homogeneous solutions. The list which follows is thus subject to limitations imposed by the presence of more than one phase and the selectivity parameter is subject to the unknown influence of the excess Lewis acid.

The ion stabilizing ability of the metal fluorides decreases in the series TaF_5, SbF_5? > BF_3 > TiF_4 > HfF_4. The list is again gleaned primarily from the $(I/E)_{MCP}$ and $(I/E)_{i\text{-}C_5}$ ratings of the acids. If the HF data in Table I are probed as was done with HBr to relate isomerization activity to the rate of exchange per ion one finds that the exchange is again inversely proportional to the ion concentration. The relative ion stability in HF–TaF_5 as opposed to HF–SbF_5 is uncertain and changes between the isopentane and methylcyclopentane systems, but carbonium ions appear to be much more stabilized in these solutions than in BF_3, TiF_4, or HfF_4–HF.

Since SbF_5 leads to a much more active isomerization catalyst than TaF_5 the data raise the question of why the ion stability in TaF_5–HF appears as high as it does. This might be because I/E is artificially high due to the unsuspected trapping of intermediates by the excess solid which could otherwise enter exchange reactions or alternatively because I/E in SbF_5–HF is too low. This could be caused by a rapid proton displacement reaction on the paraffins but it is difficult to assess this possibility at this time.

The BF_3–HF system appears to be substantially weaker than TaF_5–HF. In the experiments with isopentane, isomerization and exchange both appeared to proceed at very high rates. However, the apparent isomerization is very likely due to the occurrence of fast polymerization and cracking reactions of C_6 ions and C_6 olefins rather than to a unimolecular ionic rearrangement. The polymerization–cracking or disproportionation reactions are known to occur in this acid.[4] Their existence is indicated by the fact that large amounts of isobutane were formed along with the isomeric hexanes.

The relatively acidity of HF–BF_3 is better assessed from $(I/E)_{MCP}$ and the isomerization rate in this system. $(I/E)_{MCP}$ is very low and k_{iso} is about two orders of magnitude lower than TaF_5–HF. The BF_3–HF system provides an example of earlier predictions, namely, that low values of the selectivity parameter would be conducive to destabilization of ions, formation of olefins or alkylcyclopropanes, and subsequent coupling of these products with carbonium ions. The apparent acidities of the Lewis acids in HBr and HF as deduced from $(I/E)_{MCP}$ are shown in Table III.

TaF_5 offers the most important overlap between I/E determinations in HBr and HF. The general behavior of these systems is also shown by a comparison of the $(k_{iso})_A$ data in Table I of BF_3, TiF_4, and HfF_4 in HF and HBr.

Table IV
Some Physical Properties of the Liquid Hydrogen Halides

Property	HCl	Ref	HBr	Ref	HF	Ref
Mp, °C	−114.25	*a*	−86.92	*a*	−89.37	*g*
Bp, °C	−85.09	*a*	−66.78	*a*	19.51	*h*
Entropy of vaporization, eu	20.5	*a*	20.4	*a, d*	6.117	*g*
Dielectric constant	14.3 at 158.9°K 11.3 at 188.1°K	*b*	7.33 at 187.1°K	*e*	175 at 200°K 134 at 231°K 111 at 246°K	*i*
Specific conductance, ohm^{-1} cm^{-1}	3.5×10^{-9} at −85°C	*c*	1.4×10^{-10} at −83.6°C	*f*	1.4×10^{-5} at −15°C	*j*

[a] W. F. Giaugue and R. Wiebe, *J. Amer. Chem. Soc.*, 50, 101 (1928). [b] R. W. Swenson and R. H. Cole, *J. Chem. Phys.*, 22, 284 (1954). [c] G. Glocker and R. E. Peck, *J. Chem. Phys.*, 4, 658 (1936). [d] J. R. Bates, J. O. Halford, and L. C. Anderson, *J. Chem. Phys.*, 3, 531 (1935). [e] N. L. Brown and R. H. Cole, *J. Chem. Phys.*, 21, 1920 (1953). [f] M. E. Peach and T. C. Waddington, *J. Chem. Chem. Soc.*, 2702 (1963). [g] J. H. Hu, D. White, and H. L. Johnston, *J. Amer. Chem. Soc.*, 75, 1232 (1953). [h] R. L. Jarry and W. J. Davis, *J. Phys. Chem.*, 57, 600 (1953). [i] K. Fredenhagen and J. Dahmlos, *Z. Anorg. Chem.*, 178, 272 (1929). [j] K. Fredenhagen and G. Cadenbach, *Z. Anorg. Chem.*, 178, 289 (1929).

The isomerization activity of TaF_5 is markedly lower in HBr than in HF. Thus, $(k_{iso})_{i\text{-}C_5}$ is 0.028 hr^{-1} in HBr and 0.58 hr^{-1} in HF. Similarly, $(k_{iso})_{MCP}$ is 0.024 hr^{-1} in HBr and (0.55–0.72) hr^{-1} in HF. This behavior suggests that it is more difficult for a Lewis acid to function as an acid in HBr than in HF. One reason might be that HBr is more acidic and less nucleophilic than HF, thus rendering it more of a discriminating solvent than HF. Another and perhaps more important factor is that there is a large difference in solvation properties of liquid HBr and HF primarily because of differences in the dielectric constant. Table IV contains some of the physical properties of the liquid hydrogen halides.

The order of magnitude difference in the dielectric constant would be expected to facilitate the separation of ion pairs in HF whereas dissociation in HBr is highly unlikely except within polar cavities that might exist like micelles in solution. Thus, the apparent loss of acidity in HBr may be related to differences in degree of dissociation due to the bulk solvent properties.

The solvent properties of liquid HBr are similar to those of liquid HCl. In view of this and even though we have no direct comparison of Lewis acids in HBr and HCl it seems reasonable to compare the I/E values within these acids directly. On this basis we conclude that $GaCl_3$–HCl, $(I/E)_{MCP} = 5.6$, is an exceptionally strong acid system.

The I/E values also indicate that BBr_3–HBr is more acidic than BCl_3–HCl or BF_3–HBr from which we infer the Lewis acidity of BBr_3 is greater than BCl_3 or BF_3, but the relative strengths of the latter are uncertain. The results are consistent with other qualitative estimates of the acidity of the boron halides.[5]

(C) $(I/E)_{i\text{-}C_5}$ and $(I/E)_{MCP}$ Rank Acid Systems. It has already been observed that the exchange rates are a product of competing factors, changing concentration, and changing reactivity, and thus are not simply related to acid strength. Nevertheless, there are some important points to be learned from the changes in both the isomerization and exchange rates found in *i*-C_5 and MCP.

With the stronger acids, $AlBr_3$–HBr, TaF_5–HBr, TaF_5–HF, and SbF_5–HF one generally finds an increase in $(k_{ex})_{MCP}$ *vs.* $(k_{ex})_{i\text{-}C_5}$. One also finds equivalent or slightly accelerated isomerization rates, $(k_{iso})_{MCP} \geq (k_{iso})_{i\text{-}C_5}$. This behavior had previously been found with SbF_5–HSO_3F and TaF_5–HSO_3F,[1] and had been explained by assuming that reaction with methylcyclopentane leads to the formation of a higher concentration of ions than is obtained with isopentane. The cations are assumed to be intermediates in isomerization and hence a high rate is found in spite of the fact forming a high salt concentration necessarily lowers the acidity. The effect of the latter should be to accelerate the exchange.

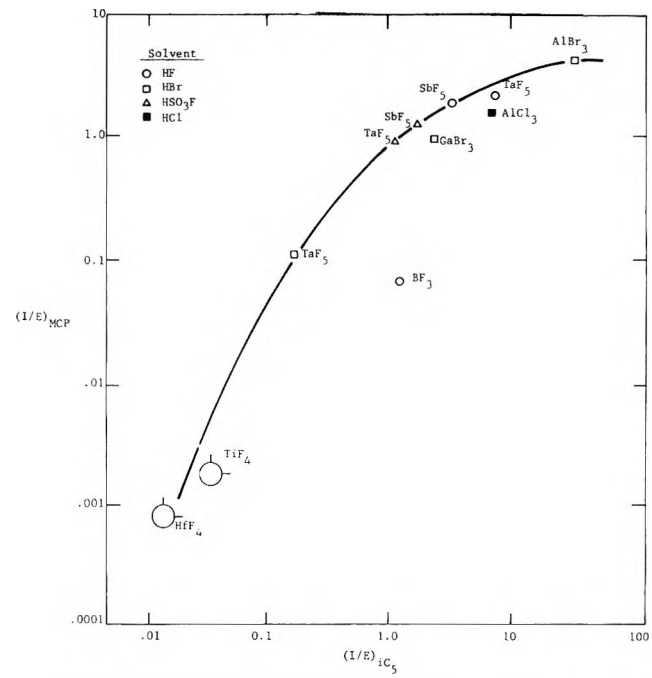

Figure 1. Correlation between the selectivity parameter in MCP and *i*-C_5.

These effects are found with the stronger acids. In the weaker acids, BF_3–HF, TiF_4–HF, and HfF_4–HF, the major effect of using MCP is to lower both the isomerization and exchange rates, the isomerization rate being most depressed. This implies that although these acids are strong enough to support the relatively stable MCP^+ ion, they are too weak for less stable tertiary alkyl cations. The observations are consistent with the view that the rate-determining step shifts from ion formation *via* hydride transfer to ionic rearrangement processes as acidity increases.

The $(I/E)_{i\text{-}C_5}$ and $(I/E)_{MCP}$ values are compared in Figure 1 where the logarithms of the ratios obtained in HBr, HF, HCl, and HSO_3F solutions are plotted against one another. The nonlinearity of the graph indicates that although some relationship exists it is not a simple free-ener-

gy relationship. This is not surprising since the change from isopentane to methylclopentane has already been surmized to change a number of factors. More important is that the graph indicates that I/E in any acid may be compared with I/E in any other acid as an index of the relative strength and ion stabilizing capacity of the system. In other words, the graph supports the proposal that I/E be used to rank acid systems.

I/E and H_0: A Limited Correlation. How do acidity scales determined by H_0 compare with the ranking of the same acids *via* the selectivity parameter? In Table V and Figure 2 comparative data for homogeneous HF, HSO_3F,

Table V

	$-H_0$[a]	$(I/E)_{i\text{-}C_5}$
HF	11.2–11.7	0
2 *M* SbF_5–HF	15.3	3.5
2 *M* TaF_5–HF, sat.	13.5	8.29
HSO_3F	14.5–15	0.42
2 *M* SbF_5–HSO_3F	>18	1.80
2 *M* TaF_5–HSO_3F	16.7	1.16
CF_3SO_3H[c]	13	0
2 *M* SbF_5–CF_3SO_3H	>18	4.25
2 *M* TaF_5–CF_3SO_3H	16.5	1.03
2 *M* NbF_5–CF_3SO_3H		<0.58
0.5 *M* SbF_5–HF	15.1	2.60
0.5 *M* TaF_5–HF	13.5	1.35
0.5 *M* NbF_5–HF, sat	~13.5[b]	0.54

[a] H_0 values were determined using indicators proposed by R. J. Gillespie and T. E. Peel, *Advan. Phys. Org. Chem.*, **9**, 1 (1971); *J. Amer. Chem. Soc.*, **93**, 5083 (1971); **95**, 5173 (1973). [b] From conductivity: H. H. Hyman, L. A. Quarterman, M. Kilpatrick, and J. J. Katz, *J. Phys. Chem.*, **65**, 123 (1961). [c] The CF_3SO_3H used was an aged acid.

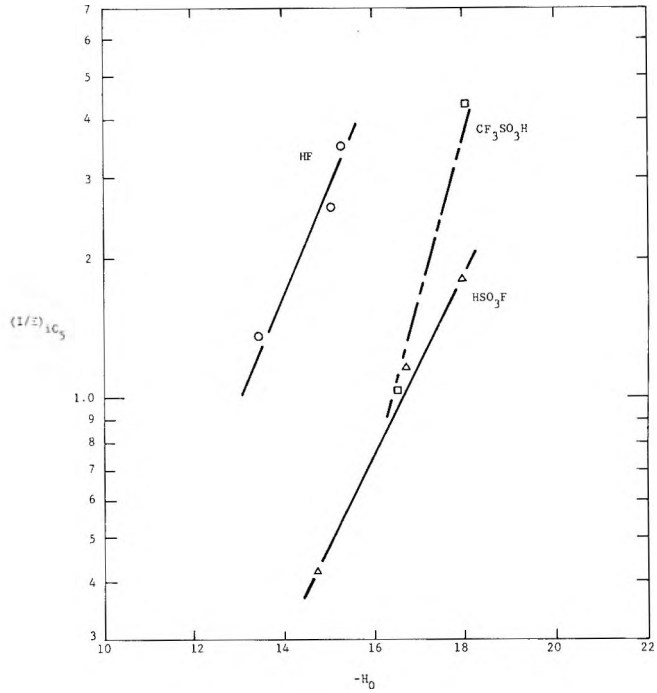

Figure 2. The selectivity parameter follows H_0 in a given acid.

and CF_3SO_3H systems are shown. It would obviously be desirable to have a more extensive set of data to better establish the relationships but it seems clear that I/E is a complex function of H_0 and the specific acid medium. Conversely, H_0 is also not a unique function of I/E.

Figure 2 suggests that in a given medium the selectivity parameter is linearly related to acidity measured by H_0 and hence a linear free-energy correlation exists. The main point, however, is that we now have an added scale to use in evaluating acidic systems. The two scales do not correlate in such a way as to permit measurements on one scale to uniquely define those on the other. This raises the immediate question of which scale is best suited for evaluating catalytic systems and which scale is best suited for evaluating acid strength. The apparent correlation of $(I/E)_{i\text{-}C_5}$ with $(I/E)_{MCP}$ described in the last section suggests that the I/E scales may provide a more consistent means of characterizing different acid systems than H_0, but they have the drawback of not being easily related to proton activity.

Table VI
Lewis Acidity Orders

Order	Method	Ref
$BF_3 > TaF_5 > NbF_5 > TiF_4 > PF_5 > SbF_3 > WF_6 >> SiF_4 \sim CrF_3$	Solvent extraction of $ArH^+MF_{n+1}^-$	6
$AsF_5 \sim BF_3 > PF_3 \sim WF_6 > NbF_5 \sim TaF_5 > SiF_4 \sim CrF_3$	Solubility of Lewis acid	7
$SbF_5 > AsF_5 > BF_3 > PF_5$	Decomposition of complex	8
$AsF_5 > PF_5 > BF_3$	Displacement reaction	9
$BF_3 = SbF_5 = AsF_5 = PF_5 > GeF_4 > TeF_6 > InF_5 > SeF_4$	Salt formation	10
$AsF_3 > BF_3 > SiF_4 > AsF_5 > PF_3$	F^- transfer from SF_6^-	11
$AsF_5 > PF_5 > BF_3 > SiF_4 > AsF_3 > SF_4$, SF_5	Ion cyclotron spectroscopy	3
$SbF_5 > TaF_5 > NbF_5$; $BF_3 > TiF_4 > HfF_4$	Selectivity parameter	1
$SbF_5 > TaF_5 \simeq NbF_5$	Conductivity	12
$SbF_5 \sim PF_5 > BF_3$	Solvolysis constants salt formation	13
$SbF_5 > AsF_5 = BF_3 > PF_5 = SnF_4 = ReF_6 = WF_6 = MoF_6 = VF_5 > IF_5 = TeF_6 = GeF_4 = TaF_5 = NbF_5 > SeF_4 = SiF_4 = TiF_4 > SbF_3 = AlF_3 = CrF_3 = BeF_2$	Solubility, salt formation	14

The relative acidities of metal fluorides determined in these studies may be compared with Lewis acidity orders from previous investigations. This is done in Table VI.

The data indicate a general agreement in the ranking to be deduced from a large variety of techniques. It is not our intention to review these studies but simply to indicate that the selectivity parameter is quite consistent with a large body of information.

Summary

Selectivity parameter measurements have been made on a series of 2 *M* mixtures of metal bromides and fluorides in HBr and HF. The Lewis acids have been ranked in the order $AlBr_3$ > $GaBr_3$ > TaF_5 > BBr_3 > BF_3, TiF_4, and HfF_4 in HBr and TaF_5 SbF_5? > BF_3 > TiF_4 > HfF_4 in HF. The order is based on the ability of the system to support isomerization relative to proton exchange. It is subject to the unknown effect of comparing homogeneous with heterogeneous systems, and the fact that the selectivity parameter for SbF_5 and TaF_5 in HF inverts as the concentration of the Lewis acid increases is an unresolved puzzle.

The Lewis acids tend to exhibit a higher selectivity parameter in HF than in HBr. This is attributed mainly to the enormous difference in dielectric constant and hence dissociative tendencies in the solvents. This overcomes the fact that HBr is more acidic than HF and therefore is a more discriminating rather than a leveling solvent.

The $(I/E)_{i\text{-}C_5}$ scale was found to be related to $(I/E)_{MCP}$, with measurements being compared in different Brønsted acids. This suggests that these scales may provide a basis for comparing the acidity or at least the catalytic activity of Lewis acids in varied media like HBr, HF, and HSO_3F.

The I/E scale in any one acid appears to correlate with H_0 but since the correlation depends on the solvent one cannot use I/E to predict H_0 in an unknown solvent or, *vice versa*, one cannot use H_0 to infer the ion stabilizing properties of the acid.

Registry No.—HBr, 11035-10-6; $AlBr_3$, 7727-15-3; $GaBr_3$, 13450-88-9; TaF_5, 7783-71-3; BBr_3, 10294-33-4; TiF_4, 7783-63-3; BF_3, 7637-07-2; HfF_4, 13709-52-9; HF, 7664-39-3; SbF_5, 7783-70-2; HCl, 7647-01-0; $GaCl_3$, 13450-90-3; $AlCl_3$, 7446-70-0; BCl_3, 10294-34-5; HSO_3F, 7789-21-1; CF_3SO_3H; 1493-13-6; NbF_5, 7783-68-8.

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Solvolysis in Dipolar Aprotic Media.[1] I. Production of Water-Extractable Bromide *vs.* Olefin Distribution in the Course of the Solvolysis of 2-Bromo-2-methylpentane in Dimethylformamide

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An investigation about the kinetics of the solvolysis of 2-bromo-2-methylpentane (1) in DMF was conducted using different titration procedures, following distributive extraction between CCl_4 and water, and gas chromatography. The reaction picture allowed division into distinct phases. The last of these is dominated by an autocatalytic second-order elimination with a notable Saytzeff character (94%) for which kinetic parameters could be estimated. The initial phase shows a remarkable instantaneous release of titrable bromide until a given level is reached; this is attributed largely to the formation of un-ionized species, probably ion pairs. Elimination in this phase has a less pronounced Saytzeff orientation (40–50% terminal olefin) and is thought to be mostly a secondary process, probably succeeding to the formation of a cationic intermediate $(RDMF)^+$ by solvent substitution. Radiobromide experiments showed a rapid incorporation of ^{82}Br into a CCl_4-extractable form, which was completely inhibited by growing C_{Br^-}, and a slower one which remained unaffected.

Solvolysis in aprotic media of alkyl halides and related compounds, carrying good leaving groups, has, on the whole, received only little attention. With a few exceptions, the scanty data available[2,3] have been obtained in view of an extension of solvent–reactivity correlations. In view of the well-established properties of DAS[4] (substantial ionizing power, high nucleophilicity and basicity, etc.) a more probing investigation was justified.

In 1957 Ross and Labes[3b] determined some first-order rate constants for the hydrogen halide production from *t*-BuCl, dimethylneopentylcarbinyl chloride, and *t*-BuBr in DMF (and *N*-methylpropionamide). Kornblum and Blackwood[3a] had already noted a halide ion production by several alkyl halides in DMF. Among these was *t*-BuBr, but also there were MeI and benzyl bromide, the latter two being unable to decompose by elimination. In neither study has an elucidation of the elimination or of the salt-forming mechanism been attempted.

In this paper the decomposition of 2-bromo-2-methylpentane (1) in dimethylformamide (DMF; ϵ_{25} 36.7) is described, as studied by (a) different distributive extraction procedures, using carbon tetrachloride and water, and (b) gas chromatography. Radiobromide incorporation has been followed under comparable conditions.

Experimental Section

Materials. Dimethylformamide (DMF, Fluka Puriss) was dried on Molecular Sieves 4A (Merck) and fractionated *in vacuo* (5 mm) from P_2O_5 (Merck p.a.), as described by Ritchie and Megerle.[5] A specific conductivity below 4×10^{-7} mho was used as the criterion for the collection (under dry nitrogen) of the usable fractions. 2-Bromo-2-methylpentane (1) was generated (bp 70° (100 mm)) from 2-methyl-2-pentanol and PBr_3 at −20°. The alcohol itself was prepared by Grignard reaction from propyl bromide and acetone. Other reagents were available commercially and purified by standard methods.

Methods. Kinetic measurements were made by analyzing aliquots (1–2 ml) taken at appropriate times from the thermostated reaction mixture (usually 65–200 ml), contained in a closed vessel. The crude sampling was done with a syringe through an inert septum, and, after quenching at 0°, a known amount (1 or 2 ml) was withdrawn with a calibrated pipet and transferred to a mixture of 5 ml of CCl_4 and 10 ml water at 0° (method A). After energetic and prolonged shaking, the phases were separated by centrifuging (3000 rpm).

In some experiments the sample was first added to the same amount of CCl_4 and the mixture was stored at 0° for 5 min before extraction with water (method B). This allowed the recombination of some DMF-solvated species that are subject to rapid hydrolysis, but it left unaffected the inorganic bromide which had been formed. Longer residence times did not improve the results. Initially 0.05 *M* aqueous NaOH was used instead of water, but this was found to be superfluous.

Titration Procedures. Both bromide and hydrogen ions were titrated potentiometrically with aqueous $AgNO_3$ and NaOH. For dilute solutions the end point was established by Gran linearization.[6]

Olefin determinations in the organic layer were sometimes carried out by an adaptation of the method of Colter and Johnson,[7] consisting in the addition of bromine (1 or 2 ml of 0.200 *M* aqueous KBr–$KBrO_3$, 5 ml of acetic acid, and 2 ml of 6 *N* sulfuric acid per 5-ml sample), conversion of the excess into iodine with aqueous KI (5 ml, 1 *N*), and titration with 0.1 *N* thiosulfate after 30 sec. With actual samples from the reaction mixtures, a stable end point could not be obtained, probably due to the presence of unreacted tertiary alkyl bromide. This of course severely limits the quantitative interpretation of these results, as olefin concentrations may have been underestimated by as much as 10–20%. Improvement on the current procedure has not been undertaken, however, as only semiquantitative use was made of these results in confirming a trend established by other means.

Gas Chromatographic Determinations. Separation of the olefins was effected on a 6-m column filled with 17% Apiezon L on Gas-Chrom P (80–100 mesh) at 50°, using hydrogen as the eluent. Before the analysis, the sample was fractionated at water-tap vacuum, through a small Vigreux-like column, for 20 sec (when only product distribution was to be determined). To measure olefin yields, cyclohexene was added as an internal standard. In these cases, fractionation had to be prolonged for 3 min to ensure quantitative transfer of the standard. Since this resulted in the distillation of a minor part of the substrate, which was found to show some decomposition on the column, the method could not be confidently used to determine low reaction yields. Before and after the treatment, samples were stored in liquid nitrogen.

Radiobromide Incorporation. $^{82}Br^-$ was commerically available from SCK (Mol, Belgium) as an aqueous solution of ammonium bromide. The original solution (4 ml) was evaporated to near dryness (approximately 0.1 ml) and a stock solution was made by addition of 1 ml of DMF. Of this, amounts of 20–100 (exceptionally 500) μl were added to 65 ml of DMF solution in actual experiments. The extra amount of water thus introduced into the reaction medium may be estimated as 30–150 ppm, the lower value being related to the more important results at high specific activity. Total activity amounted to approximately 0.08 μCi/ml in all experiments.

Except for the addition and ultimate assay of radioactive material, the design of the experiments was identical with that of the above kinetic runs followed by distributive extraction between water and CCl_4.

The samples were counted in a well-type scintillation detector, equipped with a NaI crystal (Tracerlab P-20 C). Corresponding organic and aqueous samples were always counted in immediate succession, thereby obviating the need for corrections for ^{82}Br decay, as only activity ratios were wanted. These were obtained from the mean of three determinations after correction for dead time and for volume differences.

Experiments were carried out with substrate concentrations of approximately 0.1 *M*, with and without addition of NaBr (approximately 0.2 *M*).

Treatment of Kinetic Data. Generally, the reaction picture obtained was too complex to be amenable to kinetic analysis. In some experiments, however, standard kinetic analysis was used to show trends or to estimate some rate constants.

Dominance of autocatalytic reactions was demonstrated by plotting $\log x/(a - x)$ against time, where a is the initial substrate concentration and x is the bromide ion concentration, as calculated from the titration results, which clearly differs[8–10] from the true $[Br^-]$.

When excess Br^- is added, the above consideration applies only to a lesser extent. Dissociation of the formed HBr will probably be suppressed to a high degree. Consequently, estimation of k_{2,Br^-} was here carried out on the basis of pseudo-first-order kinetics, which allowed easy correction for true first-order solvolysis.

The values stated have not been corrected for incomplete dissociation of NaBr. A crude estimate, based on a published value of pK_{diss}[11] and a simple Debye–Hückel correction leads to $\alpha = 0.87$.

Results

Reaction Picture. The reaction has been studied under varying conditions of initial substrate concentration (in the range 0.07–0.5 *M*) and temperature.

Figure 1 exemplifies the general appearance of the course of solvolysis as followed by bromide titrations (method A) and gc. The notable concurrence of both types of measurements indicates that elimination is the sole net process of the main part of the reaction. The striking variation of the olefin distribution during the reaction, however (Figure 1b), implies that in fact *several different elimination mechanisms are operative.* We found that generally, three consecutive phases could be distinguished: (a) the initial phase, characterized by the occurrence of an almost instantaneous release of titrable bromide followed by a rapid levelling off, manifesting at most a small rise in concentration of the same, and by a rather unexpectedly high, though falling, initial percentage of terminal olefin (≳50% 2-methyl-1-pentene); (b) a phase of transition, where bromide production appears to be resumed and which may include a first-order elimination as the major feature, with a regiospecificity of approximately 40% 1-olefin; (c) the autocatalytic phase, where the data are reasonably well amenable to treatment by autocatalytic kinetics. In this last case a pronounced Saytzeff orientation is noted.

The Autocatalytic Elimination (Phase c). In view of the now well-known basicity of halide ions in aprotic media, limiting E2-type eliminations, caused by Br^-, and most probably HBr_2^-, too, are not unexpected, as these ions are generated in the solution. Comparable reactions have recently been studied[12] and were identified as E2C, as designated by Winstein, Parker, and their coworkers.[12a]

At a $C_{0,substr}$ of approximately 0.46 *M* our present data are reasonably well in agreement with autocatalytic kinetics from 25 to 90% conversion at 30 and at 45° and from 45 to 90% at 60°. In fact, perfect agreement is not likely because of the fact that the titration results are not really proportional to C_{Br^-} and because of the expected importance of HBr_2^- ions and the attendent elimination reaction.

Estimates for $k_{E2,30}$ of the reaction

$$Br^- + RBr \longrightarrow \text{olefins} + Br^- + HBr$$

have been obtained, by use of method A and H^+ titration, the reaction mixture containing, besides 1 ($C_0 \simeq 0.1$ *M*), also NaBr ($C_0 \simeq 0.1$–0.2 *M*). The estimated mean of 3.8×10^{-4} sec^{-1} mol^{-1} compares well with the rate constant of related E2C reactions of halide ions in DMF and acetone.[12b,13] It is in accord also with the apparent rate con-

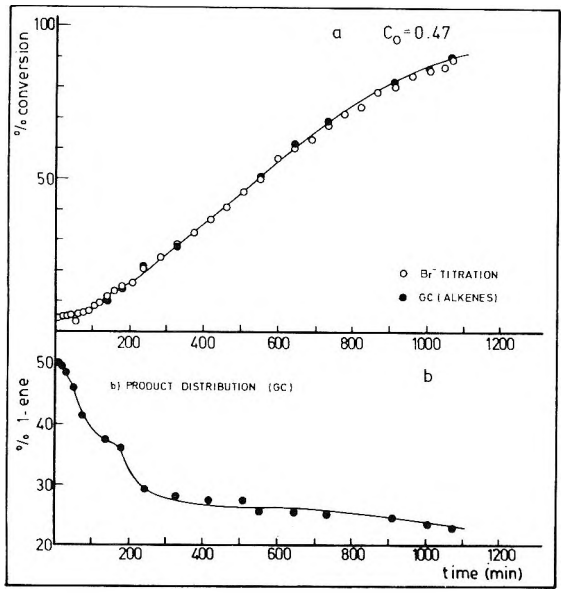


Figure 1. (a) Course of solvolysis of 1 (C_0 = 0.47 *M*) in DMF at 30.0°, as measured by bromide titration and gc (olefin determinations). (b) Attendent olefin distribution (gc).

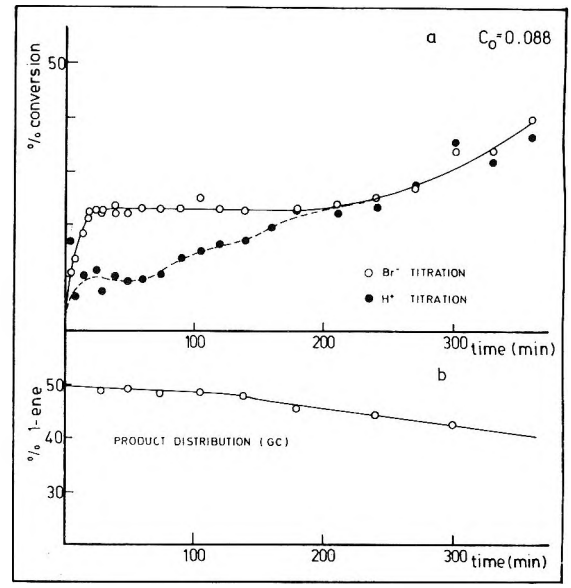


Figure 2. (a) Course of solvolysis of 1 (C_0 = 0.088 *M*) in DMF at 30.0°, as measured by Br^- and H^+ titration. (b) Attendent olefin distribution (gc).

stant $k_{E2,app,30} = 1.4 \times 10^{-4}$ sec^{-1} mol^{-1} for the autocatalytic phase of solvolysis ($C_{0,1}$ = 0.46 *M*), taking into account incomplete dissociation of HBr etc. Addition of 10^{-2} *M* picric acid does not affect the reaction rate.

The regiospecificity for this phase was determined by adding an even more substantial amount of NaBr ($C_{NaBr} \simeq$ 0.5 *M*, C_1 = 0.1 *M*). An essentially constant product orientation of 16.1 ± 0.5% 1-olefin was obtained over the whole course of reaction (and was equally unaltered by addition of 10^{-2} *M* picric acid).

Conceivably, when smaller substrate concentrations (*e.g.*, of the order of 0.1 *M*) are used, the relative importance of the autocatalytic part of the reaction in solvolysis is decreased and its dominance is postponed. These conditions evidently are more convenient for the study of the genuine solvolytic phenomena.

The Initial Phase (Phase a). This part of the reaction picture offers some rather unusual features; *viz.*, an immediate and fast rise of titrated bromide, suddenly followed by a very marked leveling off (Figure 2a). This aspect is most readily observed at lower temperatures, *e.g.*, 30°. In the experiments at 45° its occurrence is reduced to a "shoulder" and can only be conjectured at 60°. The use of substrate concentrations in a range of 0.07–0.1 *M* allows the observation of an almost constant level of apparent C_{Br^-}, for more than 200 min (!) as evidenced by Figure 2a. Under these conditions, *this steady-state* C_{Br^-} *amounts to more than 20% of the total bromide*, although its absolute value remains of the order of 0.02–0.025 *M* in all experiments. However unusual, these results stand not alone in the literature. Winstein, *et al.*,[14] gave a cursory description of an analogous albeit less pronounced phenomenon, observed after dissolving *t*-BuBr in acetone, however, without explanation. The similarity of the substrate and the dipolar aprotic character of the solvent induce us to believe that in these media this behavior is of some generality.

On the supposition that acid production itself could in any way have brought about the leveling off, picric acid was added, which at the concentration used (10^{-2} *M*), is completely dissociated.[9] In fact, the image of the experiment is greatly changed. Bromide titration now shows a slow, linear increase, although still starting at a level of 0.007 *M* which

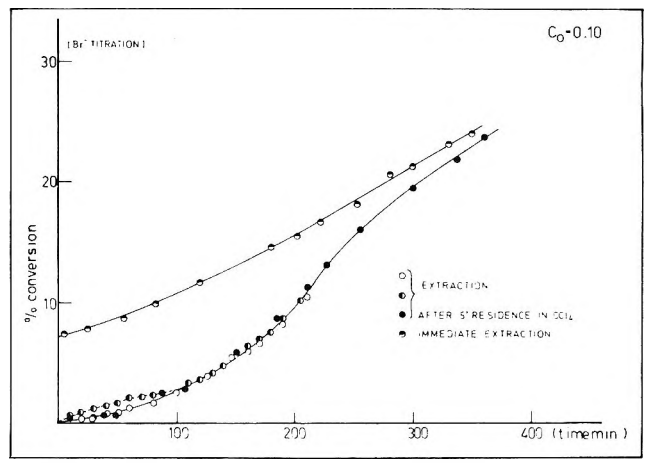


Figure 3. Course of solvolysis of 1 (C_0 = 0.10 *M*) in DMF at 30.0°, in the presence of 0.01 *M* picric acid. The lower curve represents results obtained by method B (5-min residence time in CCl_4, prior to water extraction); the upper curve represents results obtained by method A (immediate distributive extraction with a water–CCl_4 mixture).

seems to have been formed instantaneously, right at the start of the solvolysis. The lowering (from 22 to 7%) is more suggestive for a salt effect than for inhibitory action.

A refined extraction method was then devised (method B) whereby the samples were given a residence time of 5 min in CCl_4 before extraction with water. Figure 3 (lower curves) establishes that the instantaneous release of titrable bromide is due, not to HBr or its ionization products, *but to some species able to recombine in a medium of low ionizing power* while being subjected, on the other hand, to immediate hydrolysis during water extraction. It would appear to us that some kind of ion pair is the species most likely to display this behavior. In the course of the reaction, part of the recombinable bromide may well be present as free ions, provided a cationic solvolysis product is formed simultaneously. The lower curve may then be identified with the total elimination. Its sigmoidal shape and the low initial rate suggest that, at least in this phase of the reaction, the elimination consists largely, if not wholly, of a secondary process. The important primary process may then be thought of as a first-order substitution by the solvent to

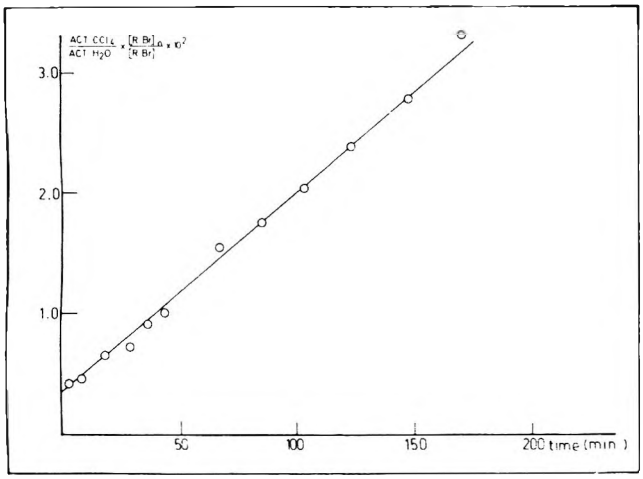


Figure 4. Incorporation of added $^{82}Br^-$ into a CCl_4-extractable form during Br^--induced E2 elimination of 1 in DMF at 30.0° (C_0 = 0.097 *M*; C_{NaBr} = 0.207 *M*; approximately 0.08 μCi ^{82}Br/ml). Relative activities of CCl_4 and water layers after distributive extraction were corrected, as shown, for substrate decomposition.

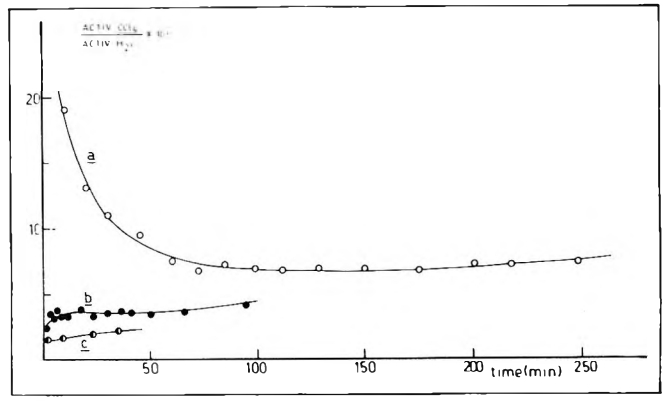
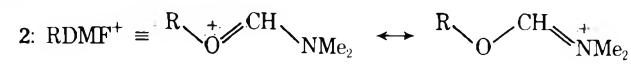


Figure 5. Incorporation of added $^{82}Br^-$ (approximately 0.08 μCi/ml) into a CCl_4-extractable form, during solvolysis of 1 (C_0 = 0.080 *M*) in DMF at 30.0°. Indicated are the relative activities of the layers after distributive extraction, with CCl_4 and water, of solvolysis samples. Total activity added per volume was almost equal, but, due to decay, "chemical" concentration of added Br^- was approximately 2×10^{-7} *M* (a), 1×10^{-6} *M* (b), and 5×10^{-6} *M* (c) in successive experiments.

yield a cationic intermediate of probable structure $RDMF^+$ (**2**)[15-18]



This is in accordance with the observation of Kornblum and Blackwood[3d] that halide ion was liberated from methyl iodide and from benzyl bromide in DMF.

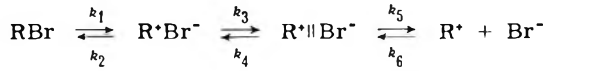
In fact, several of our own experiments demonstrate that acid and olefin production are lagging behind bromide formation. In a consistent manner, titration for Br^- gave higher results than acid determinations. Figure 2a shows an outstanding example. Olefin titrations, though less quantitative, confirm these data. Noteworthy is the fact that, in all cases studied, the resuming of apparent bromide production coincided with the disappearance of any appreciable difference in analysis results.

Olefin distribution of this phase is shown in Figure 2b. Starting at approximately 50% 1-ene, this value is slowly lowered to 46% 1-ene at the end of the phase. By comparable determinations with 10^{-2} *M* picric acid added ($C_{0,substr}$ = 0.096 *M*), an essentially constant amount of 41% (41.1 ± 0.8%) was found. This value may be attributed reasonably well to the elimination of intermediate **2**. The true regiospecificity may be somewhat higher still, as even here a contribution of the autocatalytic Br^--induced elimination is to be expected.[19] The initial product orientation in absence of any addition suggests that at the very start of the solvolysis still another elimination mechanism could be operative, endowed with a regiospecificity close to Hofmann direction! This characteristic probably excludes a straightforward E1[20,21] mechanism, which moreover would not be inhibited by increase of acid concentration or of ionic strength.

To our knowledge the only previous record of a product distribution attending solvolytic elimination in a dipolar aprotic solvent was made by Parker and coworkers, who noted 50% 1-ene for the elimination of *tert*-pentyl bromide in acetone at 50°.[22]

The Intermediate Region. In view of the foregoing discussion it is doubtful that this region should be considered as a phase with proper identity. Indeed, it is more likely that the apparent resuming of bromide production is nothing but the visible continuation of a process which was previously concealed by the superposition of the initially high level of ion-pair concentration. This interpretation is corroborated by fitting of the data of Figure 1 to first-order kinetics. In a log ($a - x$) *vs.* t plot this "phase" is well approximated by a straight line, which after extrapolation intersects with the ordinate at a value only slightly above log a.[23]

Radiobromide Incorporation Experiments. We have performed some experiments in order to examine the incorporation of radiobromide into a form which is to be found in the CCl_4 phase after distributive extraction with CCl_4 and water of solvolyzing DMF samples. The peculiar results, shown in Figure 5, may be used to shed some light on the possible pathways of solvolysis. A tentative explanation may be offered on the basis of the well-known Winstein ionization scheme[24]



In contrast to the situation in most protic media, recombination of the dissociated ions (k_6) may well be a very fast reaction, owing to the enhanced nucleophilicity of halide ions.[4a,b] This should allow a rapid incorporation of $^{82}Br^-$, especially if k_4 is not too small. Unhampered continuation of this process, however, would bring the major part of the activity in a CCl_4-extractable form after a short time, and this is not the case. If, however, the original quasiequilibrium value of carbenium ion concentration is very small, as can be postulated reasonably (k_6 large!), the progress of solvolysis and the production of Br^- by an independent way will soon inhibit radiobromide incorporation automatically. Indeed, if a quasiequilibrium between the components of the Winstein scheme is assumed, it follows that $[R^+] = k_5[R^+||Br^-]/k_6[Br^-] \simeq [RBr]/[Br^-]$.

The rate of incorporation of $^{82}Br^-$ is then proportional to $[RBr][^{82}Br^-]/[Br^-]$ or roughly to $1/[Br^-]$. This is in accord with the much lower initial incorporation rates, in case radiobromide of lower specific activity was used (Figure 5b and c) as this corresponded to a higher "chemical" bromide concentration.

Radiobromide addition to solvolysis mixtures (Figure 5) also discloses a more gradual incorporation at a lower rate, independent of the exceptional uptake at high specific activity and uninhibited by the growing bromide concentration. Even in reaction mixtures with 0.2 *M* NaBr present, the incorporation of $^{82}Br^-$ is nearly linear with time, after correction for the decreasing substrate concentration (Fig-

ure 4). These results may be explained by the occurrence of some sort of exchange reaction at the level of, *e.g.*, the solvent-separated ion pair. In fact, the concentration of any ion pair can be expected to be proportional to that of the substrate and the $^{82}Br^-$ activity in the water soluble form remains almost at a constant level for the duration of the experiment.

Summary and Conclusions

We believe to have demonstrated unambiguously that the main initial solvolysis product of 2-bromo-2-methylpentane in DMF consists of a cationic substitution product $RDMF^+$ (**2**), which consequently is eliminated to yield 2-methylpentenes with a regiospecificity of more than 40% terminal olefin (25% Hofmann elimination if corrected for statistical factors). In the course of solvolysis, the autocatalytic second-order eliminations, with Br^- and probably HBr_2^- as basic reagents, become the dominant reactions, at least in the concentration range studied. In accord with work on related reactions a pronounced Saytzeff orientation is found (94% including correction for statistical factors).

At low ionic strength the existence of yet another elimination mechanism is suspected.

The first phase of solvolysis is attended by the rapid formation of appreciable quantities of water-extractable species, the major part of which is tentatively identified as ion pairs. As none of the classical procedures used allows the determination of total solvolysis (*i.e.*, elimination plus substitution), no clear distinction can be made between these and $RDMF^+$ (**2**), whose formation may also be readily reversible during its stay in CCl_4 solution (procedure B).

^{82}Br experiments indicate, among other things, that ionization and dissociation reactions in the system studied were fast and reversible to a great extent.

Registry No.—**1**, 4283-80-1.

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Solvolysis in Dipolar Aprotic Media. II.[1] Initial Rates of Bromide Ion Production from Tertiary Alkyl Bromides in Dimethylformamide, Measured *in Situ*. A Proposal of a Solvolysis Scheme for 2-Bromo-2-methylpentane[2]

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A novel compensation method, based on potentiometric detection of Br^-, has been used to measure initial solvolysis rates of RMe_2CBr in DMF (R = Me, Et, Pr) with fair precision. Influences of substrate structure and of ionic strength are comparable to the same in protic solvents. Rate enhancement by added azide and lower activation energies was noted however. Complete absence of ionic additives gave rise to an unforeseen 17% enhancement of the expected rate. These data have been combined with those obtained in the foregoing paper to allow elaboration of a scheme for the solvolysis of $PrCMe_2Br$ (1) in DMF. The possible pathways are discussed in the light of the available evidence. It is concluded that free carbenium ions are mechanistically unimportant, whereas different kinds of ion pairs are probably essential intermediates. Some un-ionized water-extractable species, formed abundantly at dissolution of the substrate, do not lie on the main reaction path. Before an autocatalytic E2 mechanism with Br^- (and HBr_2^-) becomes predominant, the major process is constituted by substitution by the solvent, probably at the solvent-separated ion-pair stage, and subsequent elimination of the cationic substitution product (7).

There exist many marked differences between protic and dipolar aprotic solvents (DAS), liable to be relevant for their role in solvolytic reactions.[3] In the foregoing paper,[1] results have been described pertaining to the DMF solvolysis of 2-bromo-2-methylpentane (1). Conventional methods or adaptations thereof were used to disclose the existence of several reaction phases, including the dominance of substitution by the solvent as a primary process and the immediate initial presence of relatively large amounts of ion pairs, suggestive of their possible importance as reaction intermediates. Since direct assessment of total solvolysis had proved impossible, no distinction could be made between extractable ion pairs and the (ionic) substitution product.

The present paper describes the elaboration of a method able to measure the formation of ionized bromide as distinguishable from any ion pairs, as it is based on potentiometric detection of its concentration in the solvent itself. It has been used to measure initial solvolysis rates of a few "simple" tertiary alkyl bromides. An attempt is made to derive a solvolysis scheme for 1 in DMF, from a combination of these results with data previously obtained[1] and from calculations based upon them.

Experimental Section

Principle of the Potentiometric Method. The apparatus is composed of two identical thermostated vessels which were filled with an equal amount of the same medium, provided with an identical electrode system and connected through an electrolyte bridge. One of these serves as a reaction vessel. As the reaction proceeds, ions are liberated, to which the electrode system responds, and the potential difference is detected. Addition of concentrated titrant to the other vessel allows restoration of the original balance, allowing the evaluation of the progress of the reaction in the proper undisturbed medium.

The Electrode System. As the method was conceived to follow bromide ion production, the electrode system chosen consists of a silver electrode in contact with a solution containing 0.001 *M* $AgBr_2^-$.[4] The stability constant of this complex has been measured by a potentiometric titration method, as described previously,[5] and found to be 0.3×10^{16} and 1×10^{16} mol^{-2} $l.^2$ at 30 and 60°, respectively. It is readily calculated that the initial C_{Ag^+} at 30° amounts to 4×10^{-7} *M*. Thus catalysis by silver ion is insignificant, the more so as this concentration is still substantially lowered soon after the reaction sets in.[6]

Evaluation of the Method. Apart from the fact that the method fulfills a need by determining the bromide ion produced in the solvent, it possesses several advantages. It exhibits a true specificity, a characteristic of a potentiometric method, thus enabling measurements to be carried out in the presence of other ions, even halide ions. As it is a compensation method, an exact knowledge of the value of the stability constant of the $AgBr_2^-$ is not needed, provided it remains of the same order. Even if strong complexation with Ag^+ would occur, this can at most make the method insensitive, but once measurements can be performed, no error is introduced. The sole assumption which has to be made is that of the physical equality of both solutions. As a matter of fact, this cannot be exactly so, as only one of them receives the substrate. At small concentrations however, the organic compounds are not suspected to have a marked influence on the ion activities. A further objection may be found in the nonequivalency of the counterions, but as in our case the method was only used for bromide concentrations up to 3×10^{-3} *M*, this may be safely ignored.

Application of the method may probably be extended to the determination of other halide ions (even other anions) in DMF and in other solvents such as DMSO, HMPT, acetonitrile, and even alcohols, as suggested by literature values of stability constants of the corresponding complexes[7] and the general usability of silver electrodes in most[8] solvents. The most serious limitation of the method in its present form, resides in a certain slowness of response of the electrodes (1 min for a 10-mV jump), interfering with the measurement of fast reactions. It cannot be removed by lowering the substrate concentration indefinitely, as 10^{-5} *M* is the lower limit of concentrations that can be detected with the desired swiftness.

Description of the Apparatus. The water-jacketed reaction and titration vessels, of identical construction and volume (50 ml), possess a conical side wall and flat bottom to permit magnetic stirring. They are provided with five necks of appropriate size to allow insertion of electrodes, electrolyte bridge, nitrogen inlet, and if needed a capillary buret tip. The substrate is added by injection through a septum of silicone rubber.

The salt bridge is filled with a saturated solution of $NaNO_3$ in DMF. Liquid junction is established through the spacing between the ground conical inner surface of the bridge's stem and the ground tip of a glass rod, closing it from the inside.

Electrodes consist of a silver strip (0.5 cm^2; 0.5 mm thick) welded to a platinum wire. They are activated by dipping in 7 *N* NHO_3 with some $NaNO_3$ added. At first contact with the medium, containing 10^{-3} *M* $AgBr_2^-$, an adaption period of 10–15 min is re-

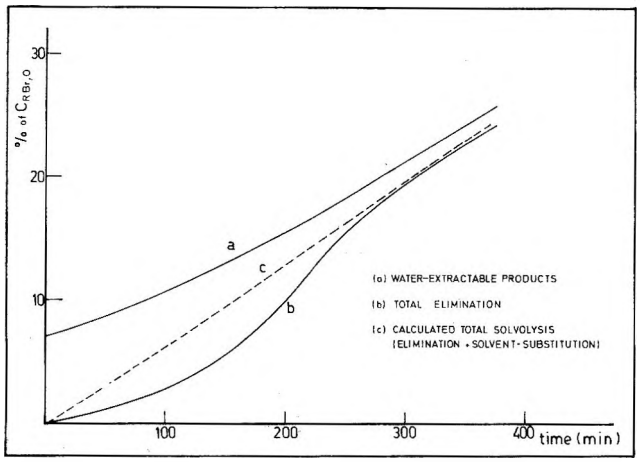


Figure 1. Comparison of experimental data (ref 1, Figure 3) on the solvolysis of 1 in DMF at 30.0° with the calculated total solvolysis (*i.e.*, total elimination plus solvent substitution). The data were obtained in the presence of 0.01 *M* picric acid.

quired, to obtain a residual potential difference of the order of 1 mV between both electrodes. As this disparity was shown to be dependent on C_{Br^-}, the electrodes are placed, at regular intervals, in the same vessel to allow comparison in the course of a kinetic run.

Measurement of potential differences was effected by means of a Radiometer Copenhagen Type PHM 22 p pH meter, as a coarse indicator and as an amplifier of high-input impedance, coupled to a recording electrometer Heath EUW-301, thus allowing recording with a precision of better than 0.03 mV if needed. A Leeds and Northrup No. 7645 potentiometer was employed to measure and to compensate the initial disparity between the electrodes.

Determination of Reaction Rates. The reaction is started by injection of an approximately known amount of substrate into the solvent in the reaction vessel, containing, besides 10^{-3} *M* $AgBr_2^-$, any additions desired. To obviate the effect of a certain sluggishness of the electrodes, addition of excess titrant is always made in advance, and the moment at which equality is reached, noted from the recording.

At the end of the run (usually not more than 3% conversion) 2-ml samples are collected and bromide ion is determined by potentiometric titration with aqueous $AgNO_3$, after alkaline hydrolysis.

First-order rate constants were directly calculated from the slopes of ln $(a - x)$ *vs.* t plots, where a is the initial substrate concentration and x is the bromide concentration in the titration vessel as derived from the known addition of titrant (0.5 *M* NaBr in DMF). No correction was applied for incomplete dissociation of HBr, as it was shown previously that the initial reaction corresponds largely to substitution in which no acid is produced.[1] From experimental tests, where formation of HBr was simulated, it was deduced that even the hypothesis of total elimination would lead to rate constants higher by only 2–3%.

Materials. Purification of the solvent and synthesis of 2-bromo-2-methylpentane have been previously reported.[1]

tert-Butyl bromide and *tert*-amyl bromide were obtained through reaction of the corresponding alcohol with PBr_3 at −20° and purified by fractionation under reduced pressure. All bromides were redistilled under reduced pressure immediately prior to use.[9]

Reliability of the Method. The method was empirically tested by titration in both vessels with the same titrant and comparison of the amounts needed to restore potential equilibrium. In the range of 2×10^{-4}–3×10^{-2} *M* the mean deviation was 0.8%. As every kinetic determination was made on the basis of at least 10 data points, it is felt that the precision obtained is still increased by the statistical distribution. The values of the standard deviations in the case of multiple determinations (*vide infra*) support this treatment.

Calculation of Total Solvolysis. An approximate calculation of total solvolysis was performed on the basis of a system composed of first-order and a second-order autocatalytic reaction

$$A \xrightarrow{k_1} X + Y$$

$$A + X' \xrightarrow{k_2} X + X' + Z$$

where A is the substrate, Y and Z are reaction products which may or may not be identical, and X′ represents the active reagent (*e.g.*, Br^-) in equilibrium with X, which summarizes all species in the same equilibrium (*e.g.*, $HBr + Br^- + \frac{1}{2}HBr_2^-$ etc.).

If a constant ratio $\alpha = C_{X'}/C_X$ is assumed, the system gives rise to the differential equations $dx/dt = dy/dt + dz/dt = k_1(a - x) + k_2(a - x)\alpha x$ or $dx/(a - x)(1 + r\alpha x) = k_1 dt$, if $k_2/k_1 = r$ and where $a = C_{A,\text{initial}}$ and x, y, and z represent concentrations of the species X, Y, and Z, and $dy = dx/(1 + r\alpha x)$. On integration these yield

$$[1/(1 + r\alpha a)] \ln [(1 + r\alpha x)a/(a - x)] = k_1 t$$

and

$$y = (1/r) \ln (1 + r\alpha x)$$

allowing calculation of x, y, and $z = x - y$. In the calculation of solvolysis (in presence of 0.01 *M* picric acid) the following values of the rate constants were utilized: $k_1 = 1.0 \times 10^{-5}$ sec^{-1} (instead of 0.97×10^{-5} sec^{-1}, to account for the small rise in ionic strength in the course of the reaction) and $k_2 = 4.0 \times 10^{-4}$ l. mol^{-1} sec^{-1}.[1]

It should be noted that in reality α is not a constant ratio and that it is not known with any certainty, due to the as yet incomplete knowledge of the ionization equilibria of HBr in DMF. Another difficulty resides in the probable importance of HBr_2^- as a major ionization product and its importance as a kinetic base, for which the corresponding rate constant k_{2,HBr_2^-} cannot be estimated. Some measurements on the HBr equilibrium and the provisional assumption $k_{2,Br^-} = k_{2,HBr_2^-}$ allow a crude estimate of $\bar{\alpha} = \bar{\alpha}_{Br^-} + \bar{\alpha}_{HBr_2^-} k_{2,HBr_2^-}/k_{2,Br^-}$ to be made. This value was altered by trial and error until the simulated curve remained between the limits set by the titration results (see Figure 1). The chosen value was 0.55, well within the range of the values estimated on the

Table I
Initial Rate Constants for Bromide Ion Production from RMe_2CBr in DMF

Entry	R	Temp, °C	C_0,[a] *M*	Additives[a]	$10^6 k_1$, sec^{-1}
1	Me	25.0	0.0390		2.3_1
2	Me	25.0	0.0412		2.1_7
3	Me	30.0	0.0375		4.2_8
4	Me	30.0	0.0385		4.2_9
5	Et	25.0	0.0332		5.2_3
6	Et	25.0	0.0482		5.1_1
7	Et	25.0	0.0482		5.1_8
8	Et	30.0	0.0342		8.5_7
9	Et	30.0	0.0345		8.4_3
10	Pr	24.8	0.0261		5.6_7
11	Pr	27.4	0.0323		7.1_6
12	Pr	29.9	0.0292		9.5_3
13	Pr	30.0	0.0317		9.6_7
14	Pr	29.9	0.0331		9.6_7
15	Pr	30.0	0.0468		9.6_0
16	Pr	30.0	0.0468		9.8_3
17	Pr	30.0	0.0470		9.6_0
18	Pr	30.1	0.1160		9.6_0
19	Pr	45.0	0.0448		47.9
20	Pr	60.0	0.0202		262
21	Pr	60.0	0.0207		245
22	Pr	30.0	0.0320		9.2_3
23	Pr	30.2	0.0336		9.8_7
24	Pr	30.0	0.0890		11.1_1
25	Pr	30.0	0.0898	0.2 *M* 2,6-lutidine	10.9_9
26	Pr	30.0	0.0309	0.1 *M* $NaNO_3$	11.3_4
27	Pr	30.0	0.0325	0.0195 *M* NaN_3	16.0
28	Pr	30.0	0.0340	0.060 *M* NaN_3	40.1
29	Pr	30.0	0.0403	0.075 *M* NaN_3	46.7
30	Pr	30.0	0.0356	0.093 *M* NaN_3	52.2
31	Pr	30.0	0.0345	0.060 *M* NaN_3 + 0.100 *M* $NaNO_3$	38.6

[a] In the presence of 0.010 *M* picric acid, except for runs 22, 23 (0.004 *M*) and 24, 25 (no picric acid added).

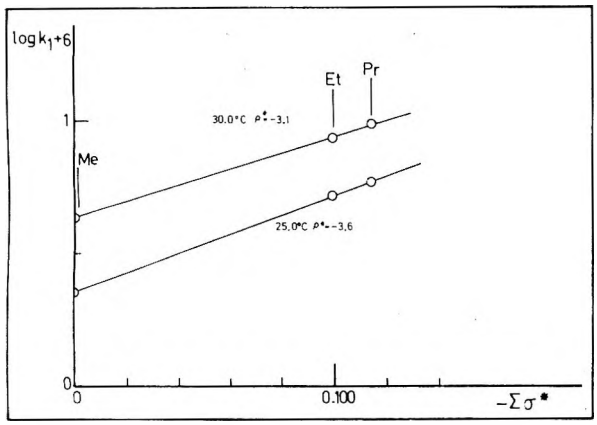


Figure 2. Taft–Hammett correlation for initial solvolysis rates of RMe_2CBr in DMF (0.01 *M* picric acid added) for R = Me, Et, Pr.

above assumptions (time average over the reaction course determined by direct estimation was found to be 0.47).

In spite of the seeming arbitrariness we feel confident that the procedure followed will not lead to large deviations from reality, as in the interval considered the total solvolysis is determined to the extent of 80–100% by the more accurately known first-order reaction. Also, bromide ion is initially the most important base formed and is suspected to remain so for appreciable time. Thus, the slope of the calculated curve fits the experimental course of the reaction very well, once the elimination becomes the sole net reaction.

Results

Reaction Rates. With the exception of two runs, all experiments have been executed in the presence of added picric acid. Apart from its promotion of electrode response, it was felt that the values obtained in this way are more likely to reflect the true rate constant in the course of the reaction, when acidity and ionic strength will have attained comparable levels. They also are directly related to the experiments in the preceding paper,[1] where addition of 10^{-2} *M* picric acid has been used.

Choice of substrate, reaction conditions, and the ensuing rate constants are summarized in Table I. Only data pertaining to the first 2–3% of the conversion have been considered for calculation. A second-order contribution to the total rate can be estimated to be at most 1% and therefore has not been corrected for.

The only value that allows comparison with literature data is for *t*-BuBr at 25.0°. It compares favorably with that reported by Kornblum and Blackwood[10] ($2.3_8 \times 10^{-6}$ sec^{-1}) and by Ross and Labes[11] (2.6×10^{-6} sec^{-1}). It was expected that our value ($2.2_4 \times 10^{-6}$ sec^{-1}) would be lowest as our measurements are confined to the first 3% of the reaction, thus excluding any important second-order contribution. Cook and Parker[12] obtained a high value ($3.3_7 \times 10^{-6}$ sec^{-1}) which can hardly be ascribed to the presence of 0.12 *M* NEt_4ClO_4, as we found only a 17% increase on addition of 0.100 *M* $NaNO_3$ in the solvolysis of **1**.

Influence of Substrate Concentration. Variation of substrate concentration by a factor 4 had no statistically significant effect on rate constants. The mean value of k_1 for runs 12–18[13] (R = Pr; temperature 30°) was found to be $(9.66 \pm 0.12) \times 10^{-6}$ sec^{-1} with substrate concentration ranging from 0.0292 to 0.1160 *M*.

Activation Energy. The activation energy E_a for the solvolysis of **1** was calculated to be 90.4 ± 0.8 kJ mol^{-1}, assuming a linear log k_1 *vs.* $1/T$ relation. The following activation parameters were found: $\Delta H^* = 87.9 \pm 0.8$ kJ mol^{-1} and $\Delta S^* = -52 \pm 4$ J K^{-1} mol^{-1}. The data of Ross and Labes[11] allow calculation of the same parameters for *t*-BuBr to give 87.4 kJ mol^{-1} and −59 J K^{-1} mol^{-1} and the rate difference is thus shown to be ascribable to an entropy effect only. The activation enthalpy in DMF is lower by a few kilojoules per mole than the corresponding parameter in pure protic solvents,[14] but comparable to it in mixed protic–aprotic solvents,[14] *e.g.*, dioxane–water and acetone–water. It may be noted in this connection that the aprotic solvents cited are known to possess nucleophilicity and could possibly participate in the transition state. We note in this context the difference in the corresponding values for acetonitrile[15] and for nitromethane;[16] 93.3 and 83.7 kJ mol^{-1}, respectively; the former is known to be a much weaker nucleophile.

Influence of Substrate Structure. Although three substrates evidently represent too small a choice to prove the existence of a linear relationship, it was thought worthwhile to represent our results in the form of a Taft correlation (Figure 2). Derived ρ^* values are −3.6 and −3.1 at 25 and 30°, respectively. They compare very well with the value −3.29 obtained by Streitwieser[17] from a huge amount of data with respect to the solvolysis of tertiary alkyl halides in 80% ethanol. It is customary to take similar values as an indication of appreciable development of positive charge on C_α in the transition state.[17,18]

Influence of Added Acid and of Ionic Strength. Reduction of the picric acid concentration from 0.010 to 0.004 *M* resulted in a decrease in reaction rate of at most 3%. This clearly demonstrates that acid catalysis can safely be excluded. That the eventual decrease is to be seen as an ionic strength effect is corroborated by the 17% increase noted, after addition of 0.1 *M* $NaNO_3$.

A similar salt effect is in accord with the theoretical expression derived by Bateman[19] for the reaction of a neutral molecule and characterized by a dipolar transition state

$$\ln (k_1/k_{1,0}) = (8\pi Ne^2/1000DkT)^{1/2} Z^2 d\alpha I$$

where e is the charge of the electron, D the dielectric constant, k the Boltzmann constant, Z the fractional charge on each pole, d the distance between them, and $\alpha = 0.509 \ln 10$. Insertion of the data yields $Z^2d = 0.97$ Å, a reasonable value, comparable to 0.78–0.82 Å found by Bateman for *t*-BuBr in 90% acetone.[19]

Solvolysis in Absence of Added Picric Acid. Extrapolating from results at different ionic strength, a value of 9.5×10^{-6} sec^{-1} should have been expected for the *initial* solvolysis rate constant of **1** at 30° in the pure solvent. The rates observed (with and without lutidine added) are 17% higher instead! Because of the simultaneous peculiarity of the product distribution, described in the preceding paper, we are inclined to interpret this difference as due to a separate reaction which seems to be inhibited at higher ionic strength.

Effect of Added NaN_3. Addition of sodium azide to solvolyzing mixtures has been used in the past to exclude the possibility of nucleophilic solvent assistance.[20] It has generally been assumed that when the strongly nucleophilic azide ion failed to enhance the reaction rate, participation of the solvent as a reagent had to be excluded also.

Runs 27–31 show in a convincing way that this is not the case in DMF even for a tertiary alkyl halide. Figure 3 shows a plot of $k_{1,N_3^-}/k_{1,0}$ *vs.* $(C_{NaN_3} - C_{picric\ acid})$,[21] where k_{1,N_3^-} is the pseudo-first-order rate constant in the presence of azide ion.

The curve obtained is reminiscent of those presented by Sneen and coworkers[22] to provide proof for the ion-pair theory of SN2 reactions. A comparable analysis will not be attempted here, as we have no precise knowledge of the ion association equilibria and some conductivity measurements on azide solutions incite us to caution. Anyway, it seems probable that azide ion participates in a second-order reac-

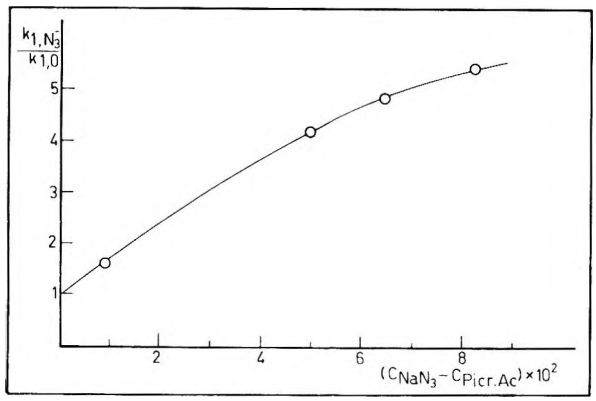


Figure 3. Influence of added sodium azide on bromide ion production from $PrMe_2CBr$ ($C_0 \approx 0.03$ *M*; 0.01 M picric acid added) in DMF at 30.0°.

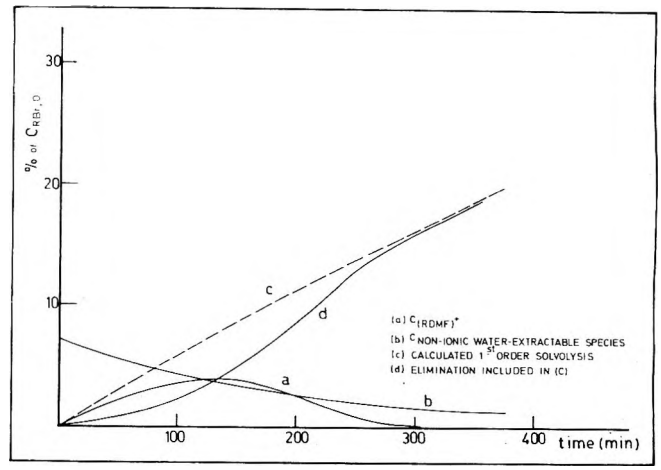


Figure 4. Analysis of the first-order component in the solvolysis of 1 in DMF at 30.0°. All curves are calculated from the data referred to in Figure 1.

tion with the tertiary substrate 1 and of which about 30–50% may be considered SN2! This cannot, of course, be used to prove solvent participation, but it emphasizes its possibility.

General Remarks. The initial solvolysis of simple tertiary alkyl bromides in DMF strongly resembles the analogous reactions in protic solvents in many of its features, *e.g.*, the dependence on substrate structure and on ionic strength. On the other hand, though no conclusive evidence was given, nucleophilic interaction between solvent and substrate would well fit the picture.

Solvolysis of 2-Bromo-2-methylpentane. Comparison of Calculated Solvolysis with Other Experimental Data. The potentiometric compensation method, described in this paper, readily follows the evolution of bromide ion concentration. As a consequence of the production of acid attending elimination and of incomplete ionization of HBr, it is only at the start of the solvolysis that the Br^- concentration can be taken to be equivalent to the total reaction rate. A direct comparison of the experimental data is therefore excluded except for the first minutes of the reaction. Even so, an interesting conclusion can be drawn with regard to the presence of appreciable amounts of "ion pairs" at the onset of the solvolysis. Further comparison is better attempted by use of the calculated course of reaction based on the determined or estimated rate constants. Figure 1 summarizes some results with respect to the solvolysis of approximately 0.1 *M* 1 in DMF at 30° and with 0.01 *M* picric acid added, as described in the previous paper.[1]

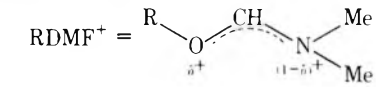
Curves a and b are based on titration data obtained after a distributive extraction with CCl_4–water, curve a prior to and curve b after a 5-min residence time in CCl_4. Curve b was thought to represent total elimination while curve a stood, in addition, for any extractable solvolysis product, ionic intermediate, *and* extractable ion pairs included. To this picture is added the calculated curve c, denoting elimination plus formation of an ionic substitution product $RDMF^+$ (7).[23]

This juxtaposition allows further insight into the details of the solvolysis, as now the evolution of the concentration of 7 can be viewed separately from that of possible ion pairs. This is shown more clearly in Figure 4 which reproduces (a) the evolution of C_7, (b) $C_{\text{"extractable ion pairs"}}$, (c) the first-order contribution to solvolysis, and (d) the part of the former curve corresponding to elimination.

In the previous paper[1] the existence of the cationic intermediate 7 has been anticipated. Figure 4 discloses that it is the principal, if not the only, initial solvolysis product. It accumulates till a maximum value of 4% of the substrate concentration. The rate of its decomposition to olefins increases steadily until most of the intermediate has disappeared.

Another notable feature is the continuous decrease of the amount of extractable "ion pairs," which is highest at very short reaction times. It cannot be estimated with confidence how much of it remains after the disappearance of 7, but it seems to be established that the rate of decrease is slowed down considerably from about that moment. Both features will be commented upon separately in the following paragraphs.

The Substitution Product $RDMF^+$ (7) and Its Decomposition. Instead of the proposed structure, 7 might be



viewed as a solvated carbenium ion. Later in this paper, however, more evidence will be presented to show the relative unimportance of dissociated carbenium ions in the overall scheme. The existence of similar substitution products has already been assumed by Kornblum and Blackwood[10] after observing halide ion production in DMF solutions of methyl iodide or benzyl bromide.[24] The formation of stable salts between solvent and alkyl halides has also been described for DMSO.[25] Moreover, nucleophilic participation of DMF is really not surprising, considering the role attributed to less nucleophilic molecules such as *p*-dioxane and acetone in the solvolyses of 2-octyl brosylate in 75% dioxane–water[26] and 80% acetone–methanol,[27] respectively.

Comparison of the slope of curve d and the corresponding values of C_7 (*a*) in Figure 4 clearly counterindicates a first-order decay of 7. Indeed, the latter curve reaches a maximum at approximately 125 min whereas curve d is steepest somewhere around the 200-min point. Therefore, kinetic involvement of a reaction product, *e.g.*, of the bromide ion, is highly probable. If we take $[Br^-]$ to be proportional to the total solvolysis, the product $[C_7][Br^-]$ has a maximum at 180 min and $[C_7][Br^-]^2$ even at 195 min, both much better in accord with the behavior of curve d.

One can think of several reasonable mechanisms, in accord with the facts known so far.

1. E2 Decomposition of 7 with Br^-. This mechanism would be reminiscent of E2 eliminations of "onium" com-

$$7 + Br^- \longrightarrow \text{olefins} + DMF + HBr$$

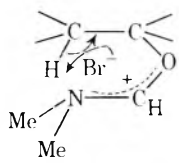
pounds. These mechanisms are known to be subject to inductive control, attended by a typical Hofmann orientation.[28] Delocalization of positive charge, as in 7, would be

expected to deemphasize this trend, so that there is no obvious disagreement with an observed product distribution of 41–46% terminal olefin.

2. First-order Elimination of the Corresponding Ion Pair 6. The situation depicted here will be kinetically equivalent to the former in a number of cases.

$$7 + Br^- \underset{k_-}{\overset{k_+}{\rightleftharpoons}} \underset{6}{7||Br^-} \xrightarrow{k'} \text{olefins} + HBr + DMF$$

If $k_- \gg k'$ the concentration of the ion pair and consequently the elimination rate are determined by the product [6][Br^-]. This version finds support in the surmise that at least a substantial fraction of the ion pairs disappeared simultaneously with **6.** If on the other hand the decomposition of the ion pair is much faster than its formation, it will not be found in measurable quantities, but the kinetic order of the elimination will remain the same with respect to **7** and Br^-. First-order elimination of **6** could very well take place *via* an "internal" mechanism akin to Ei.



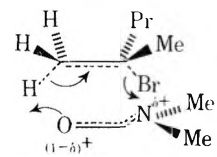
Of course, a second-order dehydrobromination of **6** or some other third-order process cannot be excluded.

Olefin distribution studies do not allow us to choose between the cited alternatives, as none is expected to possess an outspoken Saytzeff regiospecificity.[28]

Nature of the Ion Pairs. A most remarkable finding was the impressive amount of nonionic water-extractable species,[1] present in the solvolyzing DMF solution. Apparently, these particles hold strongly to the solvent molecules, as even addition to excess CCl_4 only results in a relatively slow recombination. In the course of the distributive extraction they are carried into the aqueous phase, where they are hydrolyzed subsequently.

It would appear to us that solvent-separated ion pairs are the most likely candidates to show this behavior. Part of these may be $RDMF^+||Br^-$ (**6**), as suggested above, possibly along with $R^+||Br^-$ (**3**). Neither of these, however, can be responsible for the large amount present at the very start of the reaction! In a solution of 0.1 *M* **1**, this totals 6–7% in presence of 0.01 *M* picric acid, against 22% in absence of any additive. As the solvolysis rate is not substantially different, it seems excluded that it is due to any ion pair which is to be considered as lying on the reaction path(s) leading to solvolysis. If that were the case, solvolysis kinetics would evidently be expected to be greatly influenced by the extent of its initial accumulation and by its subsequent diminution. Although satisfactory evidence is still wanting, we would like to retain, as a possible structure, the dipolar complex of the alkyl halide (or corresponding intimate ion pair) with a solvent molecule (**5**). The responsible dipole–dipole interactions may be expected to be appreciably weakened by increasing ionic strength, thus providing an explanation for the influence of added picric acid on the ion-pair concentration and for its relatively fast decrease in the course of the reaction.

Another indication for the existence of a side branch of the main pathway is to be found in *in the rapid transfer of initially incorporated* ^{82}Br *to a water-extractable form.*[1] A rate constant for this process is estimated to be at least 60 times greater than that of the solvolysis itself. This suggests that it relates to a transfer to an undissociated form and adds further credibility to the existence of the already proposed species **5.** In fact it is quite plausible that in both cases the formation of the same water-extractable species is concerned, for which the structure of a dipolar complex was proposed. One more comment can be made, *viz.*, upon the extra amount of initial solvolysis and the higher proportion of terminal olefin observed in total absence of ionic additives.[1] Both phenomena could possibly be ascribed to a direct elimination of **5,** appreciable only at the start of the reaction. For the proposed structure a way of elimination is readily conceived with the associated solvent molecule acting as a base. The transition state might resemble the structure



The ensuing syn elimination would account for a probable Hofmann orientation (possibly 70–100% 1-ene).[28]

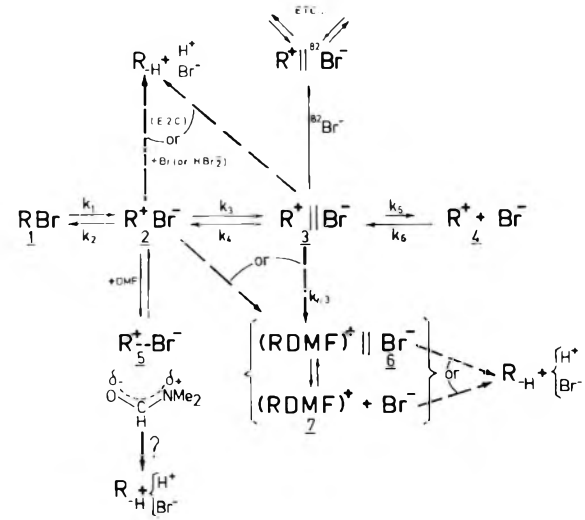


Figure 5. Solvolysis scheme for $PrMe_2CBr$ in DMF.

A Hypothetical Solvolysis Scheme for $PrMe_2CBr$ in DMF. Based on all presented evidence, we will attempt to sketch a solvolysis scheme (Figure 5) as a means of showing more clearly the emerging facts and to pinpoint some of the remaining question marks. Where alternative paths are available and no definite choice could be made, all were drawn in dashed lines. Some SN2 reactions thought to possess a common intermediate were also indicated. The *presence* of the species **5** and **6** is thought to be essential for the explanation offered, although the structures presented for them have no very firm foundation yet. The description which follows refers to the solvolysis of **1** in DMF under the conditions of our experiments, but up to a certain point probably to tertiary alkyl halides in general.

Following dissolution of the substrate, a very fast dynamic equilibrium is set up between the different species of the Winstein scheme (**1–4**).[29] The "equilibrium" concentration of dissociated carbenium ions R^+ (**4**) is thought to be much lower than in protic media and the amount of solvolysis occurring through this intermediate negligible. Solvolysis is probably attended by the ion pairs **2** and **3** reaching higher concentrations.

Especially at low ionic strength, an important accumulation of a nonionic product (**5**) is noted, to which the tentative structure of a dipolar complex has already been assigned. A relatively slow elimination of **5,** with a high yield of terminal olefin may be possible. The concentration of **5**

Table II
Solvolysis Rates of *t*-BuX (X = Cl, Br) in Different Solvents at 25.0°

Run	Solvent	$-\log k_1$ X = Cl[a]	$-\log k_1$ X = Br[b]	$-\Delta\log k_1$
1	H_2O	1.54	0.11	1.43
2	EtOH–H_2O (80:20)	5.03	3.45	1.58
3	MeOH	6.12	4.48	1.64
4	AcOH	6.71	5.52	1.19
5	EtOH	7.07	5.36	1.71
6	$MeNO_2$	8.12[c]	5.44[d]	2.68
7	DMF	8.48[e]	5.64[f]	2.84
8	MeCN	8.73[g]	5.90[h]	2.83
9	Me_2CO	9.9[i]	7.13[j]	2.8

[a] A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2770 (1956), except when indicated otherwise. [b] A. H. Fainberg and S. Winstein, *ibid.*, **79**, 1602 (1957), except when indicated otherwise. [c] Y. Pocker, *J. Chem. Soc.*, 1972 (1960). [d] P. B. D. de la Mare, *et al.*, *ibid.*, 2930 (1954). [e] S. D. Ross and M. Labes, *J. Amer. Chem. Soc.*, **79**, 4155 (1957). [f] This work. [g] M. H. Abraham, *J. Chem. Soc.*, 1343 (1972). [h] H. M. R. Hofmann, *ibid.*, 6753 (1965). [i] Cited in ref *g*. [j] S. Winstein, S. Smith, and D. Darwish, *Tetrahedron Lett.*, No. **16**, 24 (1959).

decreases rapidly as the reaction proceeds, probably by reversal of its formation, in answer to the changed environment.

At the same time a more important production of inorganic bromide accompanies the formation of the cationic product **7**, in what may be considered to be the rate-determining step. Product **7** arises probably through collapse of the solvent-separated ion pair **3**, almost certainly *via* the (likewise solvent-separated) ion pair **6**, which may be in a rapid equilibrium with **7**. Product **7** accumulates at first but undergoes in its turn an elimination reaction in a way kinetically dependent on Br^- (or possibly HBr). The increasing concentrations of Br^- and HBr_2^- cause a reaction of steadily growing importance. Being kinetically strong bases in DAS, they give rise to autocatalytic E2 with a notable Saytzeff orientation (16% 1-ene). Especially at high substrate concentration, these reactions will ultimately dominate the entire solvolysis picture.

The Insignificance of Carbenium Ions as Intermediates. To explain radiobromide incorporation data, it was postulated[1] that the concentration of free carbenium ions decreases rapidly within the first minutes of solvolysis, as a consequence of enhanced ion return caused by the growing bromide ion concentration. As an important corollary, it follows that the rate of solvolysis, if it occurred by the classical carbenium ion pathway, would simultaneously show a dramatic downfall, which is not the case at all.

The Rate-Determining Step of Solvolysis. From the incorporation experiments it was concluded that the Winstein equilibria are presumably composed of reactions which are appreciably faster than total solvolysis.[1] Therefore, they are not believed to comprise the rate-determining step. As the intermediacy of dissociated carbenium ions is excluded, the step at issue may well be the collapse of an ion pair, most probably a solvent-separated one. As a matter of fact, the latter is expected to show sufficient reactivity toward the *solvent*, almost as much as a free carbenium ion. It is likely that in this case the formation of a likewise solvent-separated ion pair **7** $\|Br^-$ (**6**) will precede the appearance of **7**. Sneen's description of an intimate ion pair, as being merely a compound possessing an extended bond with considerable ionic character,[22] does not meet universal consensus. Yet, the presence of an appreciable amount of covalent bonding is generally accepted. Consequently, the geometry at C_α may be not too remote from the original sp^3 hybridization, and in a tertiary substrate such as **1**, considerable steric hindrance to the necessarily back-side substitution is to be anticipated. These are however arguments which stem from generally accepted ideas, not from experimental data.

For solvolysis in protic media, the exact location of the rate-determining step is not generally known, although it is usually assumed to be included in the Winstein scheme. From the analysis of accurate data on the hydrolysis of *t*-BuCl, Scott and Robertson[30] suspected it to be the formation of the solvent-separated ion pair. This suggests that, even in our case, where it is not the slowest step, it may still be of great importance in determining the steady-state concentration of **3** and thereby influencing the observed rate. In this connection we wish to point out the remarkable differences in selectivity toward the leaving group, displayed in solvolysis rates, when one turns from protic to DAS media. From Table II it can be derived that in general the rate ratio $k_{t\text{-BuBr}}/k_{t\text{-BuCl}}$ is 15 times greater in the latter. The systematic way in which this difference occurs indicates a fundamental change. The fact that nucleophilic power of the solvent does not seem to be of much influence is not in contradiction with our views, as the collapse of a solvent-separated ion pair is not expected to show much selectivity with regard to the solvent. The large effect of a change in leaving group (Cl^- *vs.* Br^-) can be attributed to the position of the equilibrium **2** $\rightleftarrows$ **3**, which in DMF lies undoubtedly more to the left for the chloride ion, due to its smaller aptitude for solvation.[31]

Affinity with Sneen's Unified Ion-Pair Theory. In DMF appreciable and directly measurable quantities of different kinds of ion pairs were shown to be present during solvolysis of tertiary alkyl bromides. This alone would suffice to draw our attention to their potential role in the mechanisms involved and in related ones where these substrates are used in the same solvent. It appears to us that DAS might prove to become the media of choice for the study of ion-pair mechanisms.

In 1969 Sneen and Larsen published a unified theory of nucleophilic substitutions[32] and eliminations[33] in which they posited ion pairs to be common intermediates in all reactions cited, second order and first order alike. Since then, though, the generality of concept has been challenged;[34] several independent authors have brought forward supporting evidence in definite cases.[35]

Our analysis of the solvolysis of **1** in DMF resembles in many points the general scheme for solvolysis as presented by Sneen in a recent publication.[22] As all evidence pro and con has hitherto been obtained by use of protic (or mixed) solvents, our results clearly cannot decide in any issue in debate. The fact, however, that in a favorable solvent such as DMF solvolytic phenomena can be efficiently described in terms of mechanisms which overlap to a large extent with the scheme developed by Sneen does support its claim to a fundamental generality.

In the same recent review[22] Sneen described the probable conditions for the occurrence of a nucleophilic attack at the various points of the Winstein scheme. He thereby predicted reaction at the level of the solvent-separated ion pair to take place when the incipient carbenium ion center is rather stable and possesses a hindered back side. These are precisely the characteristics to be expected with **1** as a substrate and we are inclined to say that the prediction is borne out, at least with DMF as a solvent. Sneen and coworkers[22] made repeated use of methods in which some nucleophilic reagent (especially N_3^-) was added, and the reaction rate and selectivity were studied as a function of

its concentration. Its adaptation for use in DAS is rendered difficult by the insufficiently known association equilibria of the mostly ionic reagents, by their enhanced basicity, and by the possible reactivity of their ion pairs.

Ion Pairs as Possible Direct Substrates in E2C Reactions. Once it is accepted that ion pairs are more likely to undergo nucleophilic attack than the undissociated substrate, it may be expected that, at least in some cases, they are preferred to the latter in elimination reactions also. One might wonder if the prevalence of DAS as media for E2C reactions should not be ascribed to their proficiency at generating ion pairs. Some of the most notable characteristics of E2C,[36] such as the absolute trans elimination and a "loose" transition state, become self-explanatory, when ion pairs are considered as the direct substrates.[37,38] Research in progress in our laboratory indicates that the E2 reaction of tertiary alkyl bromides with bromide ion is competitively inhibited by added azide ion.

Registry No.—1, 4283-80-1.

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(23) Numbers were assigned to the different species and intermediates, in accordance with their place in the scheme (see Figure 5) presented in this paper, not with the chronology of appearance in the text. Product **7** is identical with structure **2** in the previous paper.[1]
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Kinetics of the Oxidative Cleavage of α-Phenylbenzoins by Alkaline Hypobromite in Aqueous Dioxane[1]

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Oxidative cleavage of α-phenylbenzoins [$Ar^1Ar^2C(OH)COAr^3$] by hypobromous acid to give benzophenones and benzoic acids has been studied kinetically in alkaline 50 vol. % aqueous dioxane. The effect of ring substituents on the rate at 25° gives ρ values of +2.8 for the σ values on Ar^3 and +2.3 for the sum of σ values on Ar^1 and Ar^2. A mechanism is postulated, which involves the formation of hypobromite ester of substrate followed by a rate-determining attack of hydroxide ion on the carbonyl carbon to give the products.

Several papers were published on the oxidation of alcohols by halogen to carbonyl compounds.[2-4] The workers in the mechanistic studies of these reactions were interested mainly in speculation of the transition state, attacking agents, and their relative reactivities. There are a number of evidences[2] that the halogen oxidation of alcohol in acidic solutions occurs *via* a rate-determining abstraction of α-hydride ion by molecular halogen. On the other hand, for the oxidation by alkaline hypohalite, the intermediacy of hypohalite ester of substrate was postulated in some oxidations of alcohols, *i.e.*, the oxidation of alcohols[3] and the oxidative decarboxylation of α-hydroxycarboxylic acids.[4]

The oxidative decarboxylation of α-hydroxycarboxylic acids by alkaline hypohalite in an aqueous solution was re-

Table I
Pseudo-First-Order Rate Constant k_{obsd} for the Reaction of α-Phenylbenzoin with Bromine in Alkaline Aqueous Dioxane (50 vol. %) at 25°

$[Br_2]_a$,[a] M	$[NaOH]_a$,[a] M	$10^4 k_{obsd}$, sec^{-1}	$[Br_2]_a$,[a] M	$[NaOH]_a$,[a] M	$10^4 k_{obsd}$ sec^{-1}
0.100	0.100	6.04	0.100	0.350	13.0
0.100	0.110	7.11	0.100	0.500	13.2
0.100	0.125	10.1	0.200	0.200	12.4
0.100	0.150	13.6	0.500	0.500	31.2
0.100	0.200	12.8			

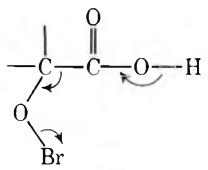
[a] Added concentration.

Table II
Relative Rate (k_{rel})[a] of the Reaction of Substituted α-Phenylbenzoins [(p-Y-C_6H_4)(p-Z-C_6H_4)C(OH)-CO(C_6H_4-W-p)] with Bromine in Alkaline Aqueous Dioxane (50 vol. %) at 25°

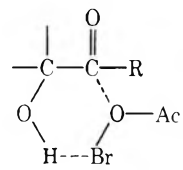
	Substituents			
Registry no.	Y	Z	W	k_{rel}[a]
4237-46-1	H	H	H	1
53432-76-1	Cl	H	H	3.73
53432-77-2	Cl	Cl	Cl	37.9
53500-16-6	H	Cl	Cl	14.0
53432-78-3	Cl	Cl	MeO	1.78
53432-79-4	H	Cl	MeO	0.460
53432-80-7	H	MeO	Cl	0.987
4338-69-6	H	H	MeO	0.178
53432-81-8	H	Me	Me	0.121

[a] $k_{rel} = k_2$(substituted)/k_2(unsubstituted). See eq 2.

ported[4] to have a mechanism[4b-d] which involves an intermediate such as A.



A



B

Donnelly and O'Donnell[5] reported that some α-ketols reacted with bromine in acetic acid to give the corresponding ketones and postulated a mechanism involving a six-membered cyclic transition state such as B because of the suppression of reaction by acetylation of hydroxy group and the necessity of the α-carbonyl group for the reaction.

The authors found that the bromine oxidation of α-ketols (α-phenylbenzoins) occurs also in alkaline solutions and is base catalyzed. The present paper describes our kinetic studies by means of glc and analysis of the reactant or product to speculate a mechanism for this reaction.

Results

Products. The reaction of α-phenylbenzoins [Ar^1Ar^2C(OH)$COAr^3$, 1] with bromine in alkaline aqueous dioxane at 25° gives the corresponding benzophenones (Ar^1Ar^2-C=O) and benzoic acids (Ar^3COOH) in good yields. Similar results were obtained with the oxidation of α-phenylbenzoin by *tert*-butyl hypochlorite in *tert*-butyl alcohol containing sodium *tert*-butoxide at 25°, while the treatment of α-phenylbenzoin with molecular bromine in dry benzene gives no benzophenone.

Rate. The rates of the reaction of α-phenylbenzoins with a mixture of bromine and sodium hydroxide in 50 vol. % aqueous dioxane (1 vol. of dioxane mixed with 1 vol. of water) at 25° were measured by following α-phenylbenzoins or benzophenones by means of glc. Bromine (0.1–0.5 *M*) and sodium hydroxide (0.1–0.5 *M*) are much more in excess to the equivalent amount of substrate (0.005 *M*) so that the pseudo-first-order plots were linear up to 50–75% conversion.

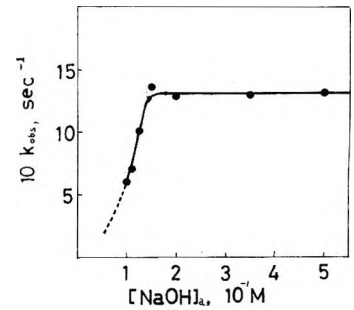


Figure 1. The effect of $[NaOH]_a$ on the rate of oxidative cleavage of α-phenylbenzoin by hypobromous acid in 50 vol. % aqueous dioxane at 25°; $[Br_2]_a$ = 0.100 *M*. Subscript a means added concentration.

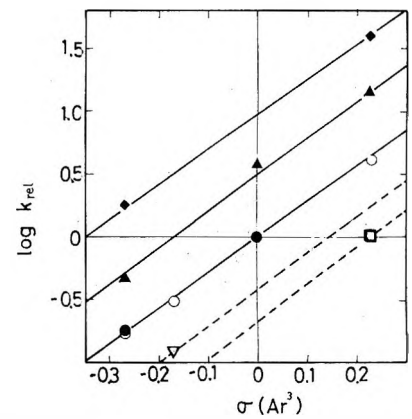


Figure 2. The plot of log k_{rel} against $\sigma(Ar^3)$ for the oxidative cleavage of α-phenylbenzoins [Ar^1Ar^2C(OH)–$COAr^3$] by hypobromous acid in 50 vol. % aqueous dioxane at 25°: ♦, $Ar^1 = Ar^2$ = p-Cl-C_6H_4; ▲, Ar^1 = Ph, Ar^2 = p-Cl-C_6H_4; ●, $Ar^1 = Ar^2$ = Ph; ▽, Ar^1 = Ph, Ar^2 = p-Me-C_6H_4; □, Ar^1 = Ph, Ar^2 = p-MeO-C_6H_4. Open circle values were obtained from the intercepts in Figure 3.

$$v = k_{obsd}[1] \quad (1)$$

The kinetic data are listed in Table I. The value of k_{obsd} is proportional to the added concentration of bromine, $[Br_2]_a$, when added sodium hydroxide concentration, $[NaOH]_a$, was equal to $[Br_2]_a$.

$$v = k_2[1][Br_2]_a \quad (2)$$

As shown in Figure 1, the rate constant increases with increasing concentration of added sodium hydroxide at lower basicity, while it holds constancy at higher basicity.

Substituent Effects. The rates for some para-substituted α-phenylbenzoins [Ar^1Ar^2C(OH)–$COAr^3$] were measured in 50 vol. % aqueous dioxane at 25°. The results are summarized in Table II. Relative rates [k_2(substituted)/k_2(unsubstituted)] are plotted against Hammett's σ. The effect of substituents on the acyl side [$\sigma(Ar^3)$] is shown in Figure 2; the plot which uses the sum of σ's for substituents on the carbinol side (Ar^1 and Ar^2) is shown in Figure 3. Assuming that the effect of substituent in Ar^1 and Ar^2 on $\rho(Ar^3)$ is negligible, the lines in Figure 2 were drawn to have the same slope. The lines in Figure 3 were drawn on the similar assumption. The intercept values at σ = 0 in

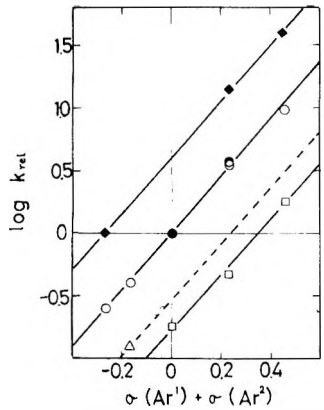


Figure 3. The plot of log k_{rel} against $\sigma(Ar^1) + \sigma(Ar^2)$ for the oxidative cleavage of α-phenylbenzoins [$Ar^1Ar^2C(OH)$–$COAr^3$] by hypobromous acid in 50 vol. % aqueous dioxane at 25°: ♦, Ar^3 = *p*-Cl-C_6H_4; ●, Ar^3 = Ph; △, Ar^3 = *p*-Me-C_6H_4; □, Ar^3 = *p*-MeO-C_6H_4. Open circle values were obtained from the intercepts in Figure 2.

Figure 2 were plotted as open circles in Figure 3; they were linear and justify the above assumption. The intercept values in Figure 3 were plotted in Figure 2 similarly and gave a straight line. These correlations give ρ values of +2.8 for σ values on Ar^3 and +2.3 for the sum of σ values on Ar^1 and Ar^2 [$\sigma(Ar^1) + \sigma(Ar^2)$].

Discussion

The oxidative cleavage of α-phenylbenzoin is favored by the presence of base. Added bromine can exist, *e.g.*, in the forms Br_2, HOBr, OBr^-, and Br_3^-, whose contents depend on the basicity of the solution.

$$Br_2 + OH^- \overset{K_3}{\rightleftharpoons} HOBr + Br^- \quad (3)$$

$$HOBr + OH^- \overset{K_4}{\rightleftharpoons} OBr^- + H_2O \quad (4)$$

$$Br_2 + Br^- \overset{K_5}{\rightleftharpoons} Br_3^- \quad (5)$$

The equilibrium constants K_3 ($[HOBr][Br^-]/[Br_2][OH^-]$ = 9.6 × 10^5)[4b,6] and K_4 ($[OBr^-]/[HOBr][OH^-]$ = 2.1 × 10^5)[4b,6] are large and the constant K_5 ($[Br_3^-]/[Br_2][Br^-]$ = 16) is fairly small, so that added bromine should be most converted to hypobromous acid (HOBr), when $[Br_2]_a$ is nearly equal to $[NaOH]_a$, and HOBr should be converted to OBr^- when $[Br_2]_a < [NaOH]_a$.

Bell-shaped pH–rate profiles were reported in the oxidative decarboxylation of α-hydroxycarboxylic acids by hypobromous acid.[4] Barker[4d] and Pink[4b,c] interpretated these phenomena by assuming that HOBr is a sole effective oxidant; *i.e.*, the rate increases with increasing concentration of HOBr at lower pH and decreases with increasing conversion of HOBr to inert OBr^- at higher pH.

Our results on the oxidation of α-phenylbenzoin by hypobromous acid in alkaline aqueous dioxane (Figure 1) are different from the case of α-hydroxycarboxylic acids; *i.e.*, the rate constant increases with increasing concentration of added NaOH at lower basic solution, while it holds constancy at higher basic solution. This suggests that the rate should be proportional to $[OBr^-]$; *i.e.*, $[OBr^-]$ increases with increasing added NaOH at lower basicity and becomes constant at higher basicity.

However, hypobromous acid, but not OBr^-, should be a more effective oxidant for this reaction of α-phenylbenzoin because of the following reasons: (i) the oxidative cleavage of α-ketols proceeds by *tert*-butyl hypochlorite in *tert*-butyl alcohol containing sodium *tert*-butoxide or by acetyl hypobromite in acetic acid,[5] where hypohalite ion (OX^-) cannot be formed; (ii) ions of Br_3^- and OBr^- are inert in the oxidation of alcohols[2,3] and α-hydroxycarboxylic acids;[4] (iii) the treatment of α-phenylbenzoin with molecular bromine in dry benzene does not yield the cleavage products.

Consequently, the rate should be expressed as

$$v = k[1][OBr^-]$$
$$= kK_4[1][HOBr][OH^-] \quad (6)$$

This suggests that the mechanism involves the participation of one molecule each of 1 and HOBr and of OH^- in a rate-determining step. These facts can be explained by a mechanism such as Scheme I.

Scheme I

$$\underset{1}{Ar^1Ar^2C(OH)COAr^3} + HOBr \overset{K_7}{\underset{\text{fast}}{\rightleftharpoons}} \underset{2}{Ar^1Ar^2C(OBr)COAr^3} + H_2O \quad (7)$$

$$2 + OH^- \xrightarrow[\text{slow}]{k_8} Ar^1Ar^2C{=}O + Ar^3CO_2H + Br^- \quad (8)$$

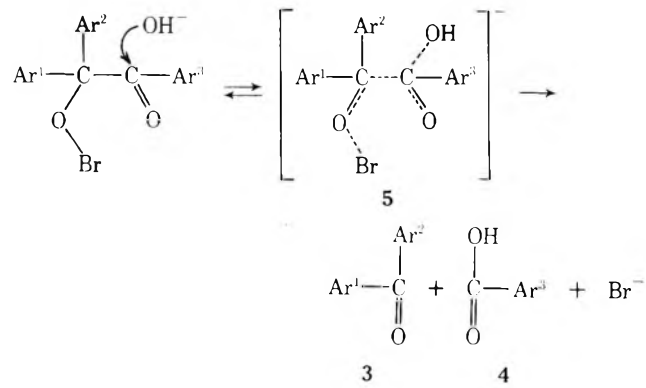
Hypobromite ester **2** formed by equilibrium 7 of substrate **1** with hypobromous acid[4] is attacked by hydroxide ion on the carbonyl carbon to give products. In this scheme, if eq 8 is a slow step, the rate should be expressed as

$$v = (k_8K_7/[H_2O])[1][HOBr][OH^-] \quad (9)$$

which is consistent with our observation (eq 6).

The observed large ρ value of +2.8 for the substituents on Ar^3 is consistent with a nucleophilic attack of a base on the carbonyl carbon. Similar results (ρ = +2–3) were reported in the nucleophilic reactions of benzoyl compounds.[7] Electron-attracting groups on Ar^1 and Ar^2 should facilitate the formation of **2** (step 7) and an attack of hydroxide ion on the carbonyl group. The large ρ value of +2.3 for the substituents on Ar^1 and Ar^2 suggests that step 8 involves a transition state as **5** in Scheme II, where the α carbon is carbanion-like. Hydroxide ion attacks the carbonyl carbon to give complex **5**, which has a carbanion-like property at the α carbon, and then bromide ion and benzoic acid are eliminated to give benzophenone. The transition states may be more polarized forming species Ar^1Ar^2C–OBr and Ar^3COOH. But it is difficult at present to decide which is the transition state.

Scheme II

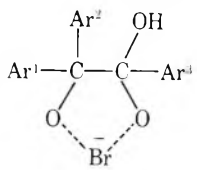


An alternative transition state is the one involving a cyclic intermediate **6**, which should give a $\rho(Ar^1, Ar^2)$ value lower than the observed ρ because of the decrease of the carbanion-like property of the α carbon.

Table III
Physical Properties of α-Phenylbenzoins [(*p*-Y-C_6H_4)(*p*-Z-C_6H_4)C(OH)-CO(C_6H_4-W-*p*)] and Elemental Analyses of New Compounds

Substituents				% calcd					% found			
Y	Z	W	Mp, °C	C	H	O	Cl	Mol formula	C	H	O	Cl
H	H	H	84.0–85.2 (lit.[10a] 83–85)									
Cl	H	H	83.5–85.0 (lit.[10b] 84)									
Cl	Cl	Cl	139–140	61.33	3.35	8.17	27.15	$C_{20}H_{13}O_2Cl_3$	61.67	3.37	9.78	26.41
H	Cl	Cl	114–116	67.24	3.95	8.96	19.85	$C_{20}H_{14}O_2Cl_2$	67.33	3.97	8.72	19.24
Cl	Cl	MeO	130–133	65.13	4.16	12.39	18.31	$C_{21}H_{16}O_3Cl_2$	65.02	4.08	11.63	18.15
H	Me	Me	Liq	83.51	6.37	10.11		$C_{22}H_{20}O_2$	83.27	6.39	9.83	
H	H	MeO	105–107	79.22	5.70	15.08		$C_{21}H_{18}O_3$	79.30	5.81	14.93	
H	Cl	MeO	Liq	71.49	4.80	13.60	10.05	$C_{21}H_{17}O_3Cl$	71.48	4.98	13.54	9.78
H	MeO	Cl	93–94	71.49	4.80	13.60	10.05	$C_{21}H_{17}O_3Cl$	71.22	4.80	13.42	9.88

Scheme II is similar to E2 elimination. The substituent effect on the rate of E2 elimination of HBr from β-arylethyl bromides ($\rho = +2.14$)[8] is fairly close to the observed values (+2.3). Further, a similar mechanism was suggested in the alkali cleavage of α-hydroperoxy ketone.[9a]



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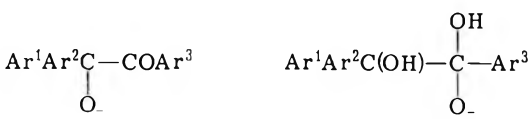
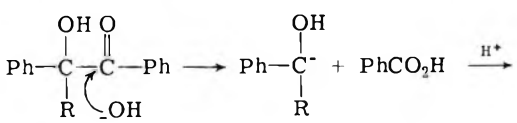
Other mechanisms, which involve the formation of intermediates such as **7a** and **7b** formed by the equilibrium of **1**



7a **7b**

with hydroxide ion followed by an attack of hypobromous acid, cannot explain the observed substituent effects described below, although they may lead to the observed rate eq 6. The observed ρ values are much larger than those predicted from the correlation of pK_a of substrate with σ, where K_a is an equilibrium constant for $\mathbf{1} \rightleftharpoons \mathbf{7a} + H^+$. An electrophilic attack of hypobromous acid would decrease further the ρ values. Moreover, the mechanism involving an intermediate **7a** would require that $\rho(Ar^1 + Ar^2) > \rho(Ar^3)$. The mechanism involving an intermediate **7b** which is formed by the OH^- attack on the carbonyl carbon would require also a smaller $\rho(Ar^1 + Ar^2)$ value than observed because of the insulation of Ar^1 and Ar^2 from the carbonyl group by the α carbon and an electrophilic attack of hypobromous acid.

Sharp and Miller[9b] reported on the alkali cleavage of α-substituted benzoins in aqueous methanol at *ca.* 60°, suggesting the mechanism



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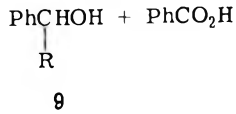

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Carbanion **8** or benzhydrol (R = Ar, **9**) should not be an intermediate in the oxidative cleavage by hypobromous acid because of the following reasons. (i) The cleavage with alkali alone, which proceeds at *ca.* 60°, cannot occur in our conditions (at 25°). (ii) The reaction of **8** with HOBr would be fast, while the observed rate depends on the concentration of HOBr. If the reaction of HOBr with **8**, which is in a mobile equilibrium with **7b**, were a slow step, the rate would be suppressed by produced Ar^3COOH in the equilibrium. (iii) No abnormal product (RCOOH) was detected, which was obtained in a considerable yield in the case of the cleavage with alkali alone.[9b]

Donnelly's mechanism should be excluded at least in an alkaline solution, since it cannot explain the rate law and substituent effect.

Experimental Section

Materials. Para-substituted α-phenylbenzoins were prepared by treatment[10] of phenyl- and *p*-chlorophenylmagnesium bromide with corresponding substituted benzils (*p*-Z-C_6H_4-CO-CO-C_6H_4-W-*p*). They were purified by recrystallizations from *n*-hexane when they were solid and by column chromatography (silica gel–benzene) when they were liquid. The substituents, melting points, and elemental analyses for new compounds of α-phenylbenzoins [(*p*-Y-C_6H_4)(*p*-Z-C_6H_4)C(OH)-CO(C_6H_4-W-*p*)] are listed in Table III. They were identified by ir spectra.

Products. α-Phenylbenzoin (0.6 g) was treated with a mixture of bromine (0.1 *M*) and sodium hydroxide (0.1 *M*) in 50 vol. % aqueous dioxane (1 vol. of dioxane mixed with 1 vol. of water) (100 ml) at 25° for 3 hr. The reaction mixture was extracted with benzene and washed with aqueous $Na_2S_2O_3$ and water. Benzophenone (0.3 g, 80%; mp 160–161°) was obtained from the organic layer and was identified by melting point, glc, and ir spectra which were consistent with those of the authentic sample. A Hitachi K-53 gas chromatograph with a flame ionization detector was used with a column packed with DEGS (13%) on Chromosorb W at the temperature increasing by 10°/min from 140 to 225° or SE-30 (3%) on Chromosorb W at the temperature increasing by 10°/min from 200 to 280° with N_2 as a carrier gas in a flow rate of 45–50 cm^3/min. Benzoic acid (0.07 g, 30%) was obtained from the aqueous layer by extraction with benzene after acidifying with aqueous HCl; mp 122°. Other para-substituted α-phenylbenzoins (Ar^1Ar^2C(OH)$COAr^3$) yielded corresponding benzophenones ($Ar^1Ar^2C{=}O$) by the similar treatments. The products were identified by glc analysis in comparison with the authentic samples which were of commercial source or were prepared from the corresponding benzhydrols.

Similar results have been obtained with the oxidative cleavage of α-phenylbenzoin with *t*-BuOCl in *t*-BuOH containing *t*-BuONa at 25°. Products were benzophenone and *tert*-butyl benzoate. On the other hand, the treatment of α-phenylbenzoin (0.1 g) with molecular bromine (0.3 g) in dry benzene (5 ml) gave no benzophene but two other products (*ca.* 5%, unknown).

Kinetics. The rate of oxidation of α-phenylbenzoins ($3.0–4.0 \times 10^{-3}$ *M*) by a mixture of excess bromine (0.1–0.5 *M*) and NaOH (0.1–0.5 *M*) at $[NaOH]_a > [Br_2]_a \gg [substrate]_0$ was measured by means of glc analysis of the remaining α-phenylbenzoins or produced benzophenones, where subscripts a and 0 mean added and initial concentrations, respectively.

A kinetic procedure was as follows. A mixture of appropriate

amounts of NaOH and Br_2 was thermostated at 25°. The reaction was started by addition of α-phenylbenzoin. At appropriate time intervals, aliquots were taken out and extracted with benzene. The contents of α-phenylbenzoin and benzophenone were measured by glc with a column packed with SE-30 as stated above. The plot of log ([substrate]$_0$/[substrate]) against time gives a straight line up to 50–75% conversion. The data were reproducible to within 5%.

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Registry No.—Bromine, 7726-95-6; dioxane, 123-91-1; hypobromous acid, 13517-11-8.

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Homoconjugation Effects in the Diels–Alder Reaction of 1-(Substituted phenyl)-3,4-dimethylenepyrrolidines

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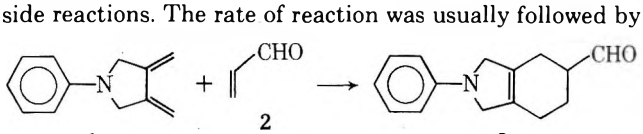
A kinetic study of the substituent effect on the diene reactivity of 1-(substituted phenyl)-3,4-dimethylenepyrrolidines in the Diels–Alder reaction was carried out. It was found that electron-withdrawing groups increased the rate of reaction and electron-donating groups decreased the rate. Hammett correlations of this substituent effect were obtained with σ n values in three solvents: methylene chloride, dimethyl sulfoxide, and tetrahydrofuran. A determination of the relative frontier orbital energies of these exocyclic dienes indicated that the effect of the substituent on the rate of the Diels–Alder reaction was primarily through a homoconjugative interaction. This interaction altered the LUMO energies of the diene causing a novel substituent effect on the reaction rate.

The effect of spiroconjugation and homoconjugation on the chemical reactivity and the electronic spectrum of spirarenes is currently of considerable interest.[1-4] It has been found that two seemingly independent π systems with a specific stereochemical relationship interact through a spatial mode such that the energies of the respective HOMO's and LUMO's are influenced. It is well known[5-10] that the HOMO and LUMO energies of the reactants in the Diels–Alder reaction can be used to predict both the reactivity and regioselectivity of this reaction. Recently Semmelhack, *et al.*,[11] have attempted to explain diene reactivity in the Diels–Alder reaction through spiroconjugative effects. In this paper, we have investigated the effect of homoconjugation on the diene reactivity of 1-(substituted phenyl)-3,4-dimethylenepyrrolidines in the Diels–Alder reaction.

Kinetic Study

The 1-(substituted phenyl)-3,4-dimethylenepyrrolidines (**1**) were allowed to react with acrolein (**2**) to give the corresponding Diels–Alder adducts (**3**) in quantitative yield (determined by nmr). The concentrations of the reactants at any given time during the reaction of the exocyclic dienes with acrolein were determined by means of nmr spectroscopy. The reaction which is shown below is uncomplicated by side reactions. The rate of reaction was usually followed by



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observing the change in chemical shift of the aldehyde proton in going from acrolein to the Diels–Alder product.[12] This change in chemical shift was 4–8 Hz depending on the solvent used and afforded distinct integrations of the area of each peak. In the cases where the change in chemical shift was not large enough to give a complete separation of the reactant and product aldehyde proton peaks, the reaction was followed by the disappearance of the vinyl peaks (δ 5.55) of the diene and the aldehyde proton peaks were used as the internal standard.

It was found that a plot of log ([acrolein]$_t$/[diene]$_t$) *vs.* time for all dienes used yielded a straight line. This linear relationship indicates that the reaction is second order overall, first order with respect to acrolein and the diene. The rate constant of the reaction was determined from the slope of the straight line as follows.

$$\text{rate constant } (k) = \frac{2.303 \times \text{slope} \times 60 \text{ sec/min}}{[\text{acrolein}]_{t=0} - [\text{diene}]_{t=0}}$$

Hydroquinone was used as an inhibitor of the polymerization of the reactants in the reaction. The concentration of hydroquinone used was usually 0.01–0.02 *M*. It was found that the concentration of hydroquinone had no effect on the observed rate constant of this reaction.

The possibility that charge-transfer interaction between the aryl group of the diene and acrolein could have an effect on the observed rate constant was investigated. The reaction of 1-(*p*-methoxyphenyl)-3,4-dimethylenepyrrolidine with acrolein was carried out with varying concentra-

Table I
Effect of Concentration Changes on the Rate Constant of the Reaction of 1-(*p*-Methoxyphenyl)-3,4-dimethylenepyrrolidine with Acrolein in Methylene Chloride at 33°

$[Acrolein]_{t=0}/[diene]_{t=0}$	Concn, *M*		Rate constant,[a,b] M^{-1} min^{-1}	Std dev
	Acrolein	Diene		
2.0:1.0	0.905	0.453	2.14	0.13
3.6:1.0	1.78	0.500	2.09	0.08
5.1:1.0	2.59	0.506	2.13	0.11
7.6:1.0	4.30	0.564	2.17	0.09

[a] Average of three kinetic runs. [b] The rate constants were determined from kinetic runs that were followed to 70–80% completion. Also, the changes in concentration had no effect on the observed rate constants when the kinetic runs were followed to 20–40% completion.

Table II
Rate Constants for the Reaction of 1-(Substituted phenyl)-3,4-dimethylenepyrrolidines with Acrolein in Methylene Chloride at 33°

Substituent	Registry no.	Rate constant, M^{-1} min^{-1}, 10^2k	Concn, *M*[a]		10^2 SD	Rel rate
			Diene	Acrolein		
p-COOEt	50872-60-1	3.50	0.471	1.84		1.67
p-Cl	32515-69-8	3.27	0.500	1.86	0.069	1.57
p-CH_3	50872-61-2	2.83	0.497	1.78	0.022	1.35
m-OCH_3	50872-63-4	2.78	0.495	1.82	0.054	1.33
H	50521-41-0	2.45	0.513	1.87	0.075	1.17
m-CH_3	50872-62-3	2.20	0.489	1.81	0.065	1.05
p-$N(CH_3)_2$	50872-58-7	2.16	0.487	1.81	0.047	1.03
p-OCH_3	50872-59-8	2.09	0.500	1.78	0.080	1.00

[a] Average of three kinetic runs for all dienes except 1-(*p*-carboethoxyphenyl)-3,4-dimethylenepyrrolidine for which one kinetic run was made.

tions of acrolein. Using an argument similar to Andrews and Keefer,[13] the rate constant should decrease in magnitude with increasing acrolein concentration if charge-transfer formation is taking place. It was found that the observed rate constants were essentially unchanged by increasing the initial dienophile to diene concentration to eightfold (Table I). Thus, it appears that no significant charge-transfer formation between acrolein and the aryl substituent took place.

These Diels–Alder reactions were carried out on a preparative scale under conditions similar to the kinetic study for three dienes (1-phenyl-3,4-dimethylenepyrrolidine, 1-(*p*-methoxyphenyl)-3,4-dimethylenepyrrolidine, and 1-(*p*-methylphenyl)-3,4-dimethylenepyrrolidine), and the adducts were isolated in near-quantitative yields (90–95%).[14] The nmr spectra of the isolated adducts were in agreement with the nmr spectra obtained from the kinetic study. The adducts were stable in a deuteriochloroform solution for several days at room temperature.

Hammett Relationship

Kinetic studies of the substituent effect on the rate of reaction of 1-(substituted phenyl)-3,4-dimethylenepyrrolidines with acrolein were carried out. In this diene system, the substituent is removed from direct conjugation with the diene portion of the molecule by a methylene group. All previous studies of the effect of substituents on the rate of the Diels–Alder reaction have employed substituents in direct conjugation with the diene.[15,16] In these prior studies, the observed effect of substituents of the diene on a normal electron demand Diels–Alder reaction was that electron-donating groups increase the rate of reaction and electron-withdrawing groups decrease the rate.

The substituent effect observed in this study, however, showed that electron-withdrawing groups increased the rate of reaction and electron-donating groups decreased the rate of reaction (Figure 1).[17] This substituent effect was

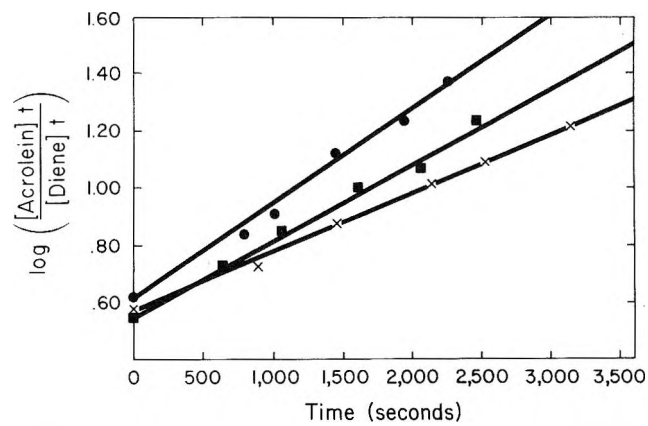

Figure 1. Diels–Alder reaction of 1-(substituted phenyl)-3,4-dimethylenepyrrolidines with acrolein in methylene chloride: (●) *p*-Cl; (X) *p*-$N(CH_3)_2$; (■) *m*-OCH_3.

observed in three solvent systems, methylene chloride, dimethyl sulfoxide, and tetrahydrofuran (Tables II and III). Hammett relationships were obtained for the reaction in these three solvents using van Bekkum's σ *n* values[18] (Figure 2). These Hammett relationships had similar ρ values and gave good correlation coefficients (Table IV). The magnitudes (0.294–0.440) of these ρ values compared favorably with the ρ value of −0.685 found for the reaction of 1-(substituted phenyl)-1,3-butadienes with maleic anhydride in dioxane.[16] These small ρ values preclude the possibility of a zwitterion intermediate[15] and support a transition state with small ionic character.

Homoconjugative Effects on Diene Frontier Orbitals

It has been shown[5-10] that the chemical reactivity can often be predicted from the frontier orbital energies of the diene and dienophile in the Diels–Alder reaction. Consequently, this approach was used to investigate this novel

Table III
Rate Constants for the Diels–Alder Reaction of 1-(Substituted phenyl)-3,4-dimethylenepyrrolidines with Acrolein in Tetrahydrofuran at 35°

Substituent	Registry no.	Solvent	Rate constant,[a] M^{-1} min^{-1}, 10^2k	Concn, M: Diene	Concn, M: Acrolein	10^2 SD	Rel rate
p-Cl		THF	1.25	0.338	1.24	0.02	1.33[b]
H		THF	1.06	0.333	1.28	0.03	1.13[b]
p-OCH_3		THF	0.941	0.378	1.13	0.04	1.00[b]
p-$N^+(CH_3)_3$	53352-46-8	DMSO	9.08	0.136	0.435	0.13	2.02[c]
H		DMSO	6.03	0.1795	0.551	0.11	1.34[c]
p-OCH_3		DMSO	4.50	0.0591	0.133	0.13	1.00[c]

[a] Average of three kinetic runs. [b] Relative rates in THF. [c] Relative rates in DMSO.

substituent effect on the diene reactivity in the Diels–Alder reaction between 1-(substituted phenyl)-3,4-dimethylenepyrrolidines and acrolein.

Since the experimental HOMO and LUMO energies are not available for the dienes in this study, INDO calculations were used to obtain relative frontier orbital energies.[19] The INDO calculations[20,21] predict an occupied frontier orbital arrangement in which the highest occupied molecular orbital (HOMO-1) of the 1-(substituted phenyl)-3,4-dimethylenepyrrolidines has mostly aniline character and the highest occupied molecular orbital with mostly diene character (HOMO-2) is of lower energy than HOMO-1 (Table V). They also predict an unoccupied frontier orbital arrangement in which the lowest unoccupied molecular orbital (LUMO-2) has mostly diene character and the lowest unoccupied molecular orbital with mostly aniline character (LUMO-1) is of higher energy than LUMO-2 (Table V).[22]

The INDO calculations yielded a trend in the frontier orbital energies of the dienes in which the orbital energies situated mostly on the aniline portion of the molecule (HOMO-1) were lowered by electron-withdrawing substituents and raised by electron-donating substituents. The effect of the aniline substituents on the HOMO-2 and LUMO-2 energies of the diene was not large enough to be seen with the INDO calculations (Table V). This is not surprising when one considers the distance between the substituent and the diene portion of the molecule.

In determining the diene reactivity, however, the energies of HOMO-2 and LUMO-2 are more important than the energies of HOMO-1 and LUMO-1 since they represent the orbitals of the diene portion of the molecule that are directly involved in the Diels–Alder reaction. Consequently, the relative trends in the frontier orbital energies of the diene portion of the molecule were determined by a perturbation molecular orbital treatment of the 1-(substituted phenyl)-3,4-dimethylenepyrrolidines. In this treatment[23] the relative energies of the frontier molecular orbitals of the 1-phenyl-3,4-dimethylenepyrrolidine were determined from an orbital interaction diagram of the frontier orbitals of aniline and cisoid 1,3-butadiene. A similar approach has been used by Simmons and Fukunaga[1] and Hoffmann, *et al.*,[2] to predict the electronic spectra and chemical reactivity of spirarenes. The orbital interaction diagram of the frontier orbitals for aniline and cisoid 1,3-butadiene was constructed from the molecular orbitals determined by INDO calculations and experimental HOMO and LUMO energies.

Table IV
Hammett Relationship of the Diels–Alder Reaction of 1-(Substituted phenyl)-3,4-dimethylenepyrrolidines with Acrolein

Solvent	ρ value	Intercept	Corr coeff	No. of points
Methylene chloride	0.440	−0.00068	0.983	7
Dimethyl sulfoxide	0.294	−0.050	0.951	3
Tetrahydrofuran	0.344	−0.0081	0.993	3

It is apparent from the orbital interaction diagram for aniline and 1,3-butadiene (Figure 3) that the interaction between the HOMO of aniline and the LUMO of the diene is the strongest. Since electron-withdrawing groups lower the HOMO energy of aniline, they will cause a weakening of the HOMO aniline–LUMO diene interaction and the resulting LUMO-2 of the 1-(substituted phenyl)-3,4-dimethylenepyrrolidines will be of lower energy than the LUMO-2 of 1-phenyl-3,4-dimethylenepyrrolidine. By similar analysis, electron-donating substituents on aniline will increase the energy of the LUMO-2 of the 1-(substituted phenyl)-3,4-dimethylenepyrrolidines relative to the unsubstituted case. The effect of the aniline group on the HOMO energy of the diene was neglected because of the large energy separation between the HOMO-2 of the diene and the LUMO-1 of the aniline.

Table V
Orbital Energies (au) of 1-(Substituted phenyl)-3,4-dimethylenepyrrolidines from INDO Calculations

Substituent	Registry no.	HOMO-2[a]	HOMO-1[b]	LUMO-1[c]	LUMO-2[d]
p-COOH	53352-47-9	−0.452	−0.373	0.124	0.113
m-OCH_3		−0.446	−0.358	0.173	0.126
H		−0.445	−0.355	0.171	0.126
m-CH_3		−0.444	−0.355	0.162	0.126
p-OCH_3		−0.446	−0.347	0.169	0.125
p-$NHCH_3$	53352-48-0	−0.443	−0.320	0.170	0.127

[a] Highest occupied molecular orbital with mostly diene character. [b] Highest occupied molecular orbital with mostly aniline character. [c] Lowest occupied molecular orbital with mostly aniline character. [d] Lowest occupied molecular orbital with mostly diene character.

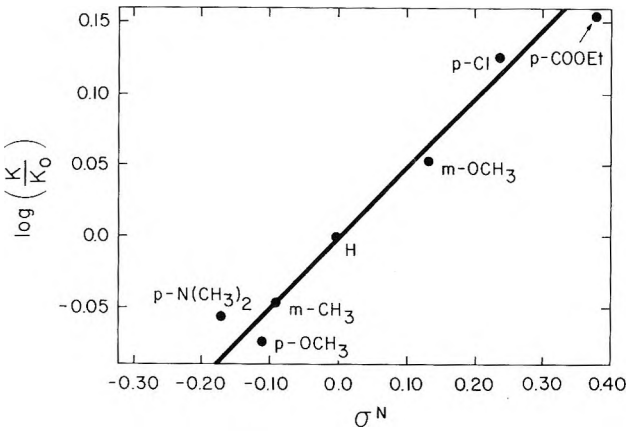

Figure 2. Hammett relationship for the Diels–Alder reaction of 1-(substituted phenyl)-3,4-dimethylenepyrrolidines and acrolein in methylene chloride.

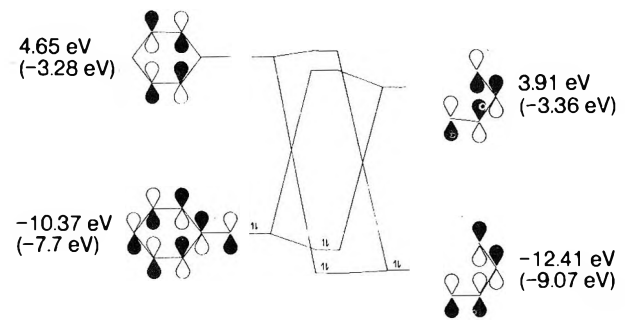

Figure 3. Orbital interaction diagram for INDO molecular orbitals of aniline and cisoid 1,3-butadiene (experimentally determined orbital energies are given in parentheses).

Frontier orbital theory predicts that the rate of the Diels–Alder reaction should increase as the energy difference between the frontier orbitals of the diene and dienophile decreases. Since electron-withdrawing substituents on the aniline cause a decrease in the energy of the aniline HOMO, these groups through homoconjugation of aniline and the diene portions of the molecule decrease the energy of the LUMO-2 relative to the 1-phenyl-3,4-dimethylenepyrrolidine case. Consequently, this decrease in LUMO-2 of the diene causes a stronger orbital interaction to take place between the HOMO of acrolein and the LUMO-2 of the diene, thus increasing the rate of Diels–Alder reaction. By similar analysis, electron donating on the aniline would decrease the rate of reaction relative to 1-phenyl-3,4-dimethylenepyrrolidine. This theoretical prediction is in direct agreement with the experimentally observed substituent effect.

Conclusion

In all prior frontier orbital studies of substituent effects on the diene reactivity of a normal electron demand Diels–Alder reaction, the effect of the substituents has been investigated through the HOMO energies (electron-donating groups increasing the rate and electron-withdrawing groups decreasing the rate). Sustmann[24] has indicated that the interaction between LUMO dienophile and HOMO diene is the dominant frontier orbital interaction and that the interaction between LUMO diene and HOMO dienophile can be neglected in determining the diene reactivity in such a Diels–Alder reaction. In this study, the unique substituent effect on the diene reactivity is caused by altering the LUMO energies of the diene through homoconjugation in contrast to Sustmann's suggestions.[24] Consequently, substituents which affect the energy of LUMO diene can have an important effect on the rate of a normal electron demand Diels–Alder reaction.

Experimental Section

Materials and Apparatus. A water bath was maintained at ±0.01° by means of a Haake E-51 temperature controller. All kinetic measurements were made on a Varian A-60 spectrometer. The accuracy of the nmr integrations was ±2.0% for the Varian A-60 and ±5.0% for the Perkin-Elmer R-24. Certified ACS dimethyl sulfoxide and tetrahydrofuran obtained from Fisher Scientific Co. were used without further purification. The methylene chloride (bp 40° (760 mm)) and acrolein (bp 52.5° (760 mm)) were distilled directly before use. All 1-(substituted phenyl)-3,4-dimethylenepyrrolidines were prepared according to the procedure reported.[14] These dienes were recrystallized in ether–petroleum ether and sublimed immediately before use. A 1-ml glass luer tip tuberculin syringe made by Becton-Dickinson was used for the measurement of solvent volumes. The accuracy of this syringe was determined to be ±0.01 ml with H_2O. Weighings were carried out on an analytical balance with an accuracy of ±0.0001 g.

Kinetic Procedure. Two different experimental procedures were used depending on the solubility of the diene.

Procedure I. An appropriate amount of the diene was weighed in a nmr tube. This nmr tube was placed, along with an air-tight vessel containing a quantitative amount of acrolein in the reaction solvent, into the constant temperature water bath and allowed to equilibrate. The bath was maintained at the nmr probe temperature. The nmr probe temperature was monitored by the use of a methanol solution. The variation found in the probe temperature was less than ±0.3°. An appropriate amount of the preheated reaction solvent (measured with a 1.0-ml syringe) was then added to the nmr tube and a timer was started. Solvation time was between 30 and 60 sec and was taken into account by subtracting one-half of the magnitude of the solvation time from the actual time the reaction was started. However, neglecting this, solvation time had no effect on the observed rate constant. During the solvation of the diene, the nmr tube was kept in the water bath, after which time it was placed directly into the nmr probe. The rate of this Diels–Alder reaction was determined by the integration of the appropriate nmr signals. Four or five integrations were taken at each time and the average value used. Usually six or seven determinations were made during each kinetic run and the reaction was followed to 70–80% completion. The volume of the reaction solution was determined by calibration of the nmr tubes. The length of the nmr tubes was calibrated with known volumes of solvent. This method was found to have an accuracy of ±1%.

Procedure II. This procedure was used for dienes whose solvation time was large enough to affect the rate constant. In this case the appropriate amount of acrolein was placed in an air-tight 10-ml volumetric flask and the appropriate amount of the diene dissolved in the reaction solution in a second air-tight 10-ml volumetric flask. The two separate solutions were brought to the reaction temperature and then mixed together. Three nmr tubes were filled with the reaction mixture and the reaction was followed by integration of the appropriate nmr peaks.

Method of Calculations. It is well known[27] that the area of an nmr absorption is proportional to the nuclei contributing to it. Thus, the area of the aldehyde peak of acrolein is proportional to the amount of acrolein present and the area of the aldehyde peak of the Diels–Alder adduct is proportional to the amount of adduct present. Using this rationale the amounts (moles) of reactants and adduct present in the reaction mixture at any given time were determined as follows.

Case I. The rate of reaction was determined by the change in chemical shift of the aldehyde proton. Let the moles of acrolein at any given time (t) be M_A. Let the initial moles of acrolein ($t = 0$) be M_{A0}. Let the area of aldehyde proton absorption of acrolein be A_A. Let the area of aldehyde proton absorption of Diels–Alder adduct be A_P. Then:

$$\frac{M_A}{M_{A0}} = \frac{A_A}{A_P + A_A}$$

$$M_A = M_{A0}\frac{A_A}{A_P + A_A} \quad (1)$$

From the stoichiometry of the chemical reaction it can be seen that for every mole of acrolein reacted a corresponding mole of the

diene must react. Let M_D equal the moles of diene at any given time (t). Let the initial moles of diene ($t = 0$) be M_{D0}. Therefore:

$$M_D = M_{D0} - (M_{A0} - M_A) \quad (2)$$

Case II. The rate of reaction was determined by the disappearance of the vinyl proton absorption (δ 5.55) of the diene. Let A_{DV} be the area of vinyl proton absorption of the diene (2 H). Let A_{AP} be the area of aldehyde proton absorptions of acrolein and Diels–Alder product (1 H). Then:

$$\frac{M_D}{M_{D0}} = \frac{A_{DV}}{2A_{AP}}\frac{M_{A0}}{M_{D0}}$$

$$M_D = M_{D0}\left(\frac{A_{DV}}{2A_{AP}}\frac{M_{A0}}{M_{D0}}\right) \quad (3)$$

$$M_D = \frac{A_{DV}}{2A_{AP}}M_{A0}$$

Therefore:

$$M_A = M_{A0}(M_{D0} - M_D) \quad (4)$$

Since the Diels–Alder reaction was carried out under constant volume conditions, the molar concentration ratios of the second-order rate equation are equal to their mole ratios (eq 5–9). Thus,

$$\log \frac{[M_{D0}]_{t=0}[M_A]_t}{[M_{A0}]_{t=0}[M_D]_t} = \frac{([M_{A0}]_{t=0} - [M_{D0}]_{t=0})^{kt}}{2.303} \quad (5)$$

$$\frac{[M_{D0}]_{t=0}}{[M_{A0}]_{t=0}} = \frac{M_{D0}}{M_{A0}} \quad (6)$$

$$\frac{[M_A]_t}{[M_D]_t} = \frac{M_A}{M_D} \quad (7)$$

$$\log \frac{M_{D0}M_A}{M_{A0}M_0} = \frac{([M_{A0}]_{t=0} - [M_{D0}]_{t=0})^{kt}}{2.303} \quad (8)$$

$$\log \frac{M_A}{M_D} = \frac{([M_{A0}]_{t=0} - [M_{D0}]_{t=0})^{kt}}{2.303} + \log \frac{M_{A0}}{M_{D0}} \quad (9)$$

integration of the appropriate nmr signals during the course of this Diels–Alder reaction allows one to determine the corresponding rate constant. The rate constant was determined from the rate equation (9) by plotting log M_A/M_D *vs.* time. The slope of this line which is equal to

$$\frac{([M_{A0}]_{t=0} - [M_{D0}]_{t=0})^k}{2.303}$$

was determined by a least-squares regression analysis.[28]

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Registry No.—Acrolein, 107-02-8.

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(23) The symmetry restrictions placed on these orbital interactions were determined by assuming that the 1-phenyl-3,4-dimethylenepyrrolidine molecule had a mirror plane of symmetry that is perpendicular to the plane of the molecule and bisects the aniline and diene portions of the molecule.
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1,8-Di-*tert*-butylnaphthalenes. Photochemistry and Mass Spectroscopy

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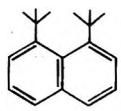
Peri di-*tert*-butylnaphthalenes have been photolyzed to afford hemi-Dewar isomers. Kinetic parameters for the thermal isomerization of the latter class of compounds have been obtained. Mass spectral data, including appearance and ionization potentials, have been obtained for the peri-crowded naphthalenes as well as their unstrained isomers.

In order to examine the conflict between steric bulk and aromatic character that is built into the 1,8-di-*tert*-butylnaphthalene system **1**, a series of photochemical and mass spectral experiments were undertaken in our laboratories.[1] The precedents for this work were developed in similar studies with the o-di-*tert*-butylbenzene system **2**.[2]



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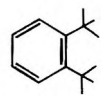
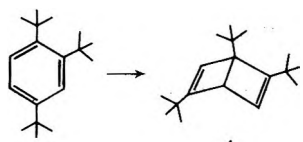


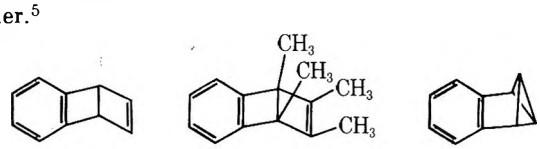
2

The seminal experiment in photochemistry and also in the field of aromatic valence isomers was that of van Tamelen and Pappas[2b] who converted 1,2,4-tri-*tert*-butylbenzene (**3**) to its Dewar isomer **4** by irradiation with Vycor-filtered uv light. Subsequent to that discovery, a systematic photochemical and synthetic research effort has succeeded in preparing and/or interconverting Dewar benzene, prismane, and benzalene isomers.

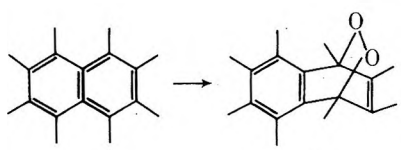


3 **4**

In the naphthalene field, the preparation of valence isomers has been largely a synthetic endeavor, and has to date afforded hemi-Dewar naphthalenes **5** and **6** and naphthvalene **7**.[3] There has been a long history of naphthalene photochemistry none of which has afforded valence isomers.[4] The most crowded naphthalene photolyzed heretofore was octamethylnaphthalene (**8**) which reacted with oxygen to form adduct **9** but exhibited no trace of valence isomer.[5]

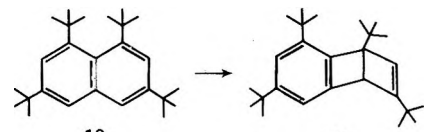


5 **6** **7**



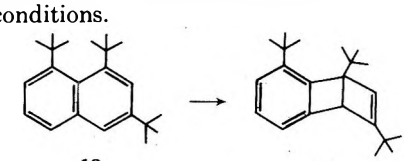
8 **9**

In our laboratory, the experiments were performed with the tetra-*tert*-butylnaphthalene **10**.[6] Irradiation in either cyclohexane or hexane using a Hanovia 450 W medium pressure lamp with Pyrex filter afforded a photoisomer **11** in 95% yield with a 5% remainder of **10**. This mixture is a photostationary state since **11**, purified by chromatography and recrystallization, afforded the same 95:5 composition upon irradiation.

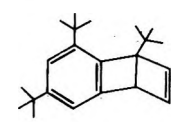


10 **11**

The structure proof of **11** is based on its nmr (*tert*-butyls at δ 1.00, 1.13, 1.30, and 1.40; benzylic H at 3.91, vinyl H at 6.10, 2 aromatic H's at 6.89 and 7.08) which compares well with that of **5**. Further, thermal isomerization (*vide infra*) of **11** afforded **10** allowing us to discount any more deep-seated rearrangement. Our study continued with tri-*tert*-butylnaphthalene **12** which afforded isomer **13** under our standard conditions.



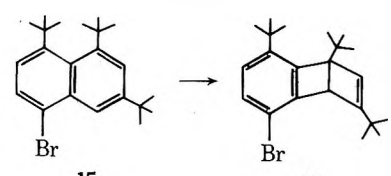
12 **13**



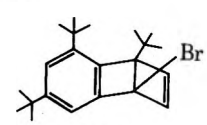
14

That the more heavily substituted ring was the one that isomerized was discerned from the nmr spectrum which had one less aromatic *tert*-butyl and one more aromatic hydrogen than that of **11**. Within the limits of analysis, we were unable to detect isomer **14**. We have no satisfactory explanation of this selectivity.

The multiplicity of the rearrangement of **10** was examined with the triplet quenchers piperylene and ferrocene (E_t 59 and 43 kcal/mol). No effect on the isomerization process was detected.[7] The bromo-*tert*-butyl derivative **15** was studied[8] with the presumption that the "heavy atom" effect[9] might allow triplet formation and perhaps some difference in photochemistry. However, the valence isomer **16** was the sole product obtained, with no evidence for **17** or any other valence isomer discernable.



15 **16**



17

The thermal reversal of the Dewar isomers was studied in some detail.[10] The rate constants for the rearomatization

Table I
Rate Constants, Half-Lives, and Activation Parameters for the Thermal Reversion of 11

Temp, °C	Rate constant, sec^{-1}	$t_{1/2}$, hr
38[a]		70
50	$1.07 \pm 0.19 \times 10^{-5}$	18.3
65	$5.8 \pm 0.8 \times 10^{-5}$	3.4
70[a]		2
80	$2.6 \pm 0.4 \times 10^{-4}$	0.75
E_a	24.0 ± 3.8 kcal/mol	
Log A	11.3 ± 2.4	

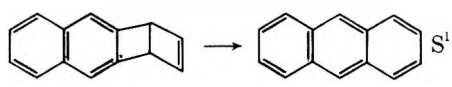
[a] Half-lives at these temperatures were computed for easy comparison to data for other valence isomers.

Table II
AP and IP Data for *tert*-Butylnaphthalenes (eV)

Isomer	AP	IP	Δ
12	7.14	9.58	2.44
24	7.76	10.36	2.60
25	7.68	10.30	2.62

of **11** were determined using nmr integration. The results are presented in Table I. Comparable half-lives were observed for isomers **13** and **16.** These indicate a higher barrier to aromatization than that for the less substituted analog **5** ($t_{1/2}$ 4 hr, 38°) and a similar barrier to that of **6** ($t_{1/2}$ 1.5 hr, 70°). One factor in the higher energy can be assigned to the effects of *tert*-butyl rotation. In the aromatic compound **10,** the barrier to free rotation is 6 kcal/mol,[6a] determined at an nmr coalescence temperature of −137°. The comparable hindrance to rotation in the Dewar isomer **11** cannot be determined at the lowest temperature of operation of the spectrometer, therefore presumably less than that of **10.**[11]

The adiabatic isomerization of electronically excited valence isomers to electronically excited states of parent aromatics has been observed recently. Naphthvalene **7** upon flash photolysis affords triplet naphthalene,[12] while anthracene valence isomer **18** affords singlet anthracene **19** upon excitation.[13] Similar experiments performed by Pro-



18 **19**

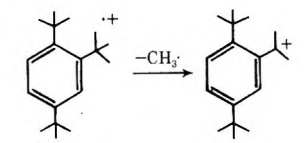
fessor Turro's group at Columbia with **11** and **16** did not yield observable aromatic excited states, presumably because these states have a dark pathway, namely valence isomerization, available for energy consumption.

From the excited states of photochemistry we turn to those of mass spectroscopy to obtain one datum desired in the 1,8-di-*tert*-butylnaphthalene series: the calorimetric strain energy as a comparison to that of the *o*-dibutylbenzenes. We chose a mass-spectroscopy method developed by Arnett.[14] He compared the increment in energy between the appearance potential of the molecular ion and the ionization potential for the M − 15 peak. When the increments in unstrained di-*tert*-butylbenzenes were compared to the increments of o-di-*tert*-butylbenzenes, it was noted that the strained cases required ~1 eV less energy which in kcal/mol compares quite favorably to the strain energy determined by calorimetry. The assumption implicit in these experiments was that a crowded *tert*-butyl group in 1,2,4-tri-*tert*-butylbenzene (**20**) loses a methyl group to form a

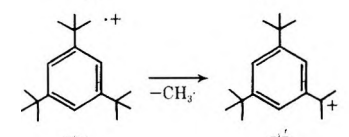
Table III
Mass Spectra (70 eV) of *tert*-Butylnaphthalenes

Peak	Probable assignment	Rel intensity	Peak	Probable assignment	Rel intensity
1,4			1,3,8		
240	M^+	76	296	M^+	100
225	M − CH_3	100	281	M − CH_3	36
183	M − *t*-Bu	14	240	M − isobutylene	8
169		10	239	M − *t*-Bu	38
167		10	238	M − isobutane	5
165		10	237		7
			226		10
1,3			225		49
240	M^+	75			
225	M − CH_3	100	1,3,5,8		
183	M − *t*-Bu	5	352	M^+	100
169		5	337	M − CH_3	44
167		6	297		16
165		8	296	M − isobutylene	66
			295	M − *t*-Bu	9
1,3,6			294	M − isobutane	12
296	M^+	100	281		75
281	M − CH_3	82			
239	M − *t*-Bu	2	1,3,6,8		
			352	M^+	100
1,3,5			337	M − CH_3	19
296	M^+	100	297		6
281	M − CH_3	55	296		25
239	M − *t*-Bu	2.5	295		2
			294		5
			281		25

dimethylbenzyl cation **21** which is not significantly more crowded than the cation **23** derived from 1,3,5-tri-*tert*-butylbenzene (**22**). Thus, any difference in energy for the loss

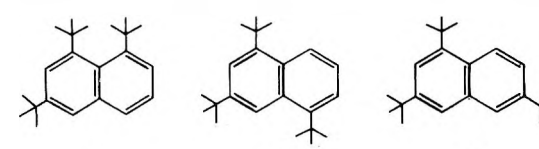


20 **21**



22 **23**

of CH_3 was assigned to a difference in ground-state energy of the isomers, namely strain energy in the more crowded **20.** This assumption hsn been analyzed more rigorously by Jalonen and Pihlaja.[15] With this precedent to encourage us, and with the 1000-fold greater quantities required for conventional combustion calorimetry to discourage us, we determined appearance potentials (AP) of the molecular ions of naphthalenes **12, 24,** and **25** and ionization potentials



12 **24** **25**

(IP) of their M − 15 fragments. The method of semilog plots of ion abundance *vs.* electron energy with krypton and acetone as calibration standards was used.[16] The results are presented in Table II.

It can be seen that the increments between AP and IP of crowded and uncrowded *tert*-butylnaphthalenes are essentially equal. Thus, the extrapolation of Arnett's technique to our series breaks down. The rationale for this nonextrapolation is simply that the nonhindered *tert*-butyl is participating in the loss of CH_3· presumably because there is insufficient relief of strain energy in the loss of methyl from a crowded *tert*-butyl group. Further, our analysis of nmr data has postulated a great deal of nonplanarity in the peri-crowded region so that the *tert*-butyls are not true "aromatic" *tert*-butyls. Thus, their interaction with radical cation of the molecular ion would not be the same as "aromatic *tert*-butyls" and they would not be forming a true planar dimethylbenzyl cation as the methyl radical was departing. This presumed lack of "reactivity" of peri *tert*-butyls finds an interesting parallel in the acid-catalyzed reactions discussed in our earlier work.

The routine 70 eV mass spectra in the series produced no unusual observations (Table III). We searched carefully for evidence of bis elimination of methyl and hydrogen or two methyls to form a less-strained ring, but no such peaks were observed. This may be contrasted to data obtained for 4,5-dimethylphenanthrene by Dougherty, *et al.*[17]

Experimental Section

Photochemistry. General Procedure. The naphthalene to be photolyzed was placed in an 8 in. long reaction vessel (capacity *ca.* 150 ml) with a 50/60 ground glass female joint and dissolved in 120 ml of spectral grade solvent. A water-cooled immersion well with a 50/60 ground glass male joint (lightly greased with Nonaq stopcock grease) containing a Pyrex filter and a 450 W, type L Hanovia high-pressure mercury lamp, catalog No. L6′, was inserted into the reaction vessel and the magnetically stirred solution subjected to photolysis. The progress of the photolysis was followed by removing a sample of the photolysate and subjecting it to uv analysis (PE-202, hexane), monitoring the disappearance (usually about 48 hr) of the maximum at *ca.* 310 nm, which is characteristic of 1,8-di-*tert*-butylnaphthalenes. The uv sample was then returned to the reaction vessel. After the photolysis was judged complete, the solvent was evaporated under reduced pressure at *room temperature* and the residue was dissolved in pentane and filtered through 1 g of activity II neutral alumina contained in a Pasteur pipet using pentane as the eluent. The pentane was evaporated at *room temperature* and the residue was used without further manipulation for the kinetic runs or other experiments.

2,4,8,10-Tetra-*tert*-butyltricyclo[4.4.0.0^{2,5}]deca-3,6,8,10-tetraene, (5,6-Benzo-1,3,7,9-tetra-*tert*-butylbicyclo[2.2.0]hexa-2,5-diene or 1,3,7,9-Tetra-*tert*-butyl Hemi-Dewar Naphthalene) (11). A sample of 0.128 g (0.363 mmol) of 1,3,6,8-tetra-*tert*-butylnaphthalene was photolyzed for 48 hr. At the end of this time the hexane was evaporated and the yellow-white solid filtered through activity II neutral alumina using pentane as the eluent. The pentane was evaporated to yield 0.128 g (100%) of a white solid shown by nmr (CCl_4) to consist of 95% photoproduct 11 and 5% starting material. The above solid (0.028 g) was recrystallized from a minimum amount of warm (45°) methanol to yield 0.009 g (32%, first crop only, the yield was not maximized) of pure (by uv) photoproduct: mp 57–58°; ir (CCl_4) 3.45, 6.87, 6.93, 7.29, 7.42, 9.19, and 11.51 μ; nmr (CCl_4) δ 1.00 (9 H, s, C_1-*tert*-butyl), 1.13 (9 H, s, C_3-*tert*-butyl), 1.30 (9 H, s, C_7-*tert*-butyl), 1.38 (9 H, s, C_9-*tert*-butyl), 3.91 (1 H, d, J = 1.5 Hz, methine H), 6.10 (1 H, d, J = 1.5 Hz, vinyl H), 6.89 (1 H, d, J = 1.5 Hz, H_7 or H_9), and 7.08 ppm (1 H, d, J = 1.5 Hz, H_9 or H_7); uv max (hexane) 273 (2.83) and 282 nm (log ϵ 2.82).

Anal. Calcd for $C_{26}H_{40}$: C, 88.57; H, 11.43. Found: C, 88.44; H, 11.41.

The same results were obtained using spectral grade cyclohexane as the solvent, or at 5° using hexane as the solvent.

2,4,10-Tri-*tert*-butyltricyclo[4.4.0.0^{2,5}]deca-3,6,8-10-tetraene (5,6-Benzo-1,3,9-tri-*tert*-butylbicylo[2.2.0]hexa-2,5-diene or 1,3,9-Tri-*tert*-butyl Hemi-Dewar Naphthalene) (13). A sample of 0.062 g (0.209 mmol) of 1,3,8-tri-*tert*-butylnaphthalene was photolyzed for 48 hr. At the end of this time, the hexane was evaporated and the yellow oil filtered through activity II neutral alumina using pentane as the eluent. The pentane was evaporated to yield 0.062 g (100%) of a colorless oil shown by nmr (CCl_4) to consist of 90% photoproduct **13** and 10% starting material. Attempts to either induce crystallization or separate the valence bond isomer by chromatography were a failure. The tri-*tert*-butyl hemi-Dewar naphthalene had the following spectral characteristics: nmr (CCl_4) δ 1.00 (9 H, s, C_1-*tert*-butyl), 1.13 (9 H, s, C_3-*tert*-butyl), 1.38 (9 H, s, C_9-*tert*-butyl), 3.97 (1 H, d, J = 1.5 Hz, methine H), 6.14 (1 H, d, J = 1.5 Hz, vinyl H), and 6.67–7.17 ppm (3 H, m aromatic H); uv max (hexane, 10% naphthalene impurity subtracted out) 272 (2.67) and 279 nm (log ϵ 2.60).

7-Bromo-2,4,10-tri-*tert*-butyltricyclo[4.4.0.0^{3,5}]deca-3,6,8,10-tetraene (16). A photolysis of 0.055 g (0.2 mmol) of 5-bromo-1,3,8-tri-*tert*-butylnaphthalene was carried out under nitrogen. After 15 hr the material was passed through a gram of activity grade II alumina with hexane elution and yielded 0.050 g (91%) of an isomer: ir (CCl_4) 1100, 1130, 1365, 1385, 1450, 1465, 1550, 2900 cm^{-1}; nmr (CCl_4) δ 7.08 (1 H, d, Ha of AB quartet, J_{AB} = 8.5 Hz), 7.04 (1 H, d, Hb of AB quartet, J_{AB} = 8.5 Hz); 6.15 (1 H, d, J = 1.5 Hz), 3.95 (1 H, d, J = 1.5 Hz), 1.40 (9 H, s), 1.18 (9 H, s), 1.09 (9 H, s).

Anal. Calcd for $C_{22}H_{31}Br$: C, 70.57; H, 8.35; Br, 21.34. Found C, 70.59; H, 8.48; Br, 21.21.

Kinetics of the Thermal Reversion of the Hemi-Dewar Naphthalenes to Naphthalenes. A sample (0.033–0.50 g) of the hemi-Dewar compound was dissolved in 0.35 ml of spectral grade CCl_4 and filtered into an nmr tube. The tightly stoppered nmr tube was then placed into a preheated oil bath at the temperature the reversion was being studied (50, 65, or 80°). The temperature of the oil bath was maintained by a Therm-O-watch temperature controller (I^2R, Model No.L-621, T = ±0.6°). At various times (about every 4–6 hr at 50°, every hr at 65°, and every 10–15 min at 80°) the nmr tube was removed from the oil bath and as quickly as possible placed into ice water for 2 min. The nmr tube was wiped free from water and as quickly as possible an nmr spectrum of the appropriate region was taken. The ratio of hemi-Dewar naphthalene and naphthalene at various times was determined by integration of the appropriate nmr signals. For the tetra-*tert*-butyl compound, the nmr spectral absorptions corresponding to the signals of the aromatic protons of the hemi-Dewar compound (δ 6.89 and 7.08) and the signals of the aromatic protons in the naphthalene (δ 7.22 and 7.48) were integrated and the ratio of areas was obtained after correcting for the number of protons. For the tri-*tert*-butyl compound, the nmr spectral absorptions corresponding to the olefin signal (6.14 δ) of the hemi-Dewar compound and the signals of the *entire* aromatic region (δ 6.67–7.6) were integrated and the ratio of areas was obtained after correcting for the number of protons. From these ratios, first-order plots were obtained (7–10 data points per run), the best straight line being determined by least-squares analysis (using a Compucorp 025 Educator calculator, program No.8802464). The rate constants and half-lives were then calculated from the slope of the straight line. Two runs were done at each of the three temperatures and the value of the rate constant (and half-life) at a particular temperature was taken as the average value of the two runs at that temperature. The average value of the rate constant at a particular temperature was then used for the energy of activation calculation. The three data points thus obtained were subjected to least-squares analysis (above) to find the equation of the best straight line from whose slope and intercept E_a and the value of log A were respectively determined.

Acknowledgment. We are indebted to Professor G. Epling of this department and Professor N. Turro of Columbia University for extensive discussions of our photochemical experiments. R.W.F. is most grateful to Lord Todd and Dr. Dudley Williams of Cambridge University for making available laboratory facilities in order to carry out the mass spectroscopy. Further, gratitude is owed to Dr. Adrian Yeo for the AP and IP measurements at Cambridge and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—**10**, 22495-86-9; **11**, 40155-12-2; **12**, 22495-89-2; **13**, 40155-13-3; **15**, 53535-11-8; **16**, 53535-12-9; **24**, 37754-74-8; **25**, 26157-41-5; 1,4-di-*tert*-butylnaphthalene, 10565-10-3; 1,3-di-*tert*-butylnaphthalene, 22495-85-8.

References and Notes

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(7) In flash experiments kindly performed by Dr. Arthur Lyons in Professor N. Turro's laboratory, no phosphorescence of the triplet state of **10** could be detected. We thank Professor Turro for permitting the disclosure of his experiments.

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(18) Commercially available chemicals were used as supplied except where noted. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Boiling points are uncorrected. Analyses were determined by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were recorded on Perkin-Elmer Model 137 and 337 spectrophotometers. Ultraviolet spectra were taken on a Cary 15 spectrophotometer. Nmr spectra were recorded on Varian A-60A and XL-100 instruments with signals reported relative to internal tetramethylsilane. The multiplicity of signals is reported as follows: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m; broad, br; envelope, ev; and exchange with deuterium oxide, ex. Analytical and preparative thin-layer chromatography was done using silica gel GF-254 and alumina GF-254, Type E, purchased from the Brinkmann Instruments Co. Florisil (60–100 mesh) was obtained from the Fisher Scientific Co. Silica gel and alumina for dry column chromtography, which was done according to the method of Loev and Goodman, *Chem. Ind. (London)*, 2026 (1967), was bought from Waters Associates. Neutral alumina, activity II, was purchased from Woelm.

Infrared Liquid-Phase Chemiluminescence from Reactions of Bis(2,4,6-trichlorophenyl) Oxalate, Hydrogen Peroxide, and Infrared Fluorescent Compounds

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Several polycyclic aromatic hydrocarbon derivatives provide infrared fluorescence quantum yields on the order of 0.30 in solution. The infrared fluorescers were combined with a peroxyoxalate chemiluminescent system based on bis(2,4,6-trichlorophenyl) oxalate to provide solution-phase infrared chemiluminescence with quantum yields as high as 0.06 einstein mol^{-1}. The effect of fluorescer concentration on chemiluminescence quantum yield indicated the theoretical maximum yield of excited emitter to be 49% with the fluorescer 16,17-dihexyloxyviolanthrone. Theoretical considerations relating to infrared fluorescence and chemiluminescence are discussed.

Infrared chemiluminescence, unlike visible chemiluminescence, is unlikely to be discovered by accidental observation, and few examples are known. The examples are confined to gas-phase reactions which produce vibrationally excited states,[1] to emission from singlet oxygen,[2] and to reaction of violanthrone with singlet oxygen.[3]

It is well recognized that efficient liquid-phase chemiluminescence requires the efficient formation of an electronically excited singlet product in a chemical reaction and that the excited product must be an efficient fluorescer.[4,5] The modification of a chemiluminescent reaction to produce emission in a specified spectral region is generally difficult, however. Most chemiluminescent reactions produce their excited products directly from the energy releasing reactants, and it is difficult to modify the structure of the fluorescent product while at the same time retaining the efficient excitation capability of the reactant.[6]

Peroxyoxalate chemiluminescence, however, differs from most chemiluminescent reactions in that the emission spectrum depends on the fluorescence spectrum of a compound which is added independently of the reactants.[7,8] Through the use of a variety of fluorescers, emission almost spanning the visible spectrum has been obtained.[7-9] This property, along with its inherent efficiency, encouraged us to select the peroxyoxalate reaction as the basis for infrared chemiluminescence research.

The peroxyoxalate reaction of bis(2,4,6-trichlorophenyl) oxalate with hydrogen peroxide and sodium salicylate was chosen because this reaction has been shown to provide quantum yields as high as 0.20 einstein mol^{-1} with the fluorescer rubrene.[10] A search of the literature for organic infrared fluorescers failed to reveal an acceptable prospect, although several dyes have been reported to luminesce in the infrared on fibers,[11] and several red fluorescers have spectral distributions extending into the infrared in solution.[12] Two useful criteria are available for fluorescer design. First, the intrinsic probability of radiative transition from an excited electronic level increases with the extinction coefficient of the electronic absorption of that level.[13] Thus, compounds having extinction coefficients above about 10^4 have a relatively high fluorescence probability. Secondly, according to Stokes' law the emission spectral distribution of an organic fluorescer in general approximates the mirror image of the absorption spectrum and

usually is displaced 50–200 nm toward longer wavelengths.[14] Thus, organic compounds having first absorption bands at wavelengths longer than 650 nm, and with extinction coefficients greater than 10^4, are potential infrared fluorescers. In general, compounds having these properties will have a rigid structure with a high degree of conjugated unsaturation, and polycyclic aromatic hydrocarbon derivatives appeared particularly attractive. Advantage was also taken of bathochromic spectral shifts produced by substituents such as alkoxy[13] and phenylethynyl[15,16] to extend the emission wavelengths of red fluorescers into the infrared.

Results

Infrared Fluorescers. The compounds investigated as fluorescers are illustrated in Chart I, and their absorption and fluorescence properties are summarized in Table I. Fluorescence spectra and quantum yields were usually measured in ethyl benzoate (EB) or o-dichlorobenzene (DCB) solutions to facilitate subsequent chemiluminescence studies, but several fluorescers were measured in benzene or (because of solubility difficulties) in 1,2,4-trichlorobenzene (TCB). Five of the 11 compounds in the table (Ib–d, IV, and VI) are predominately infrared fluorescers with emission maxima above 700 nm while the others provided appreciable red as well as infrared emission.

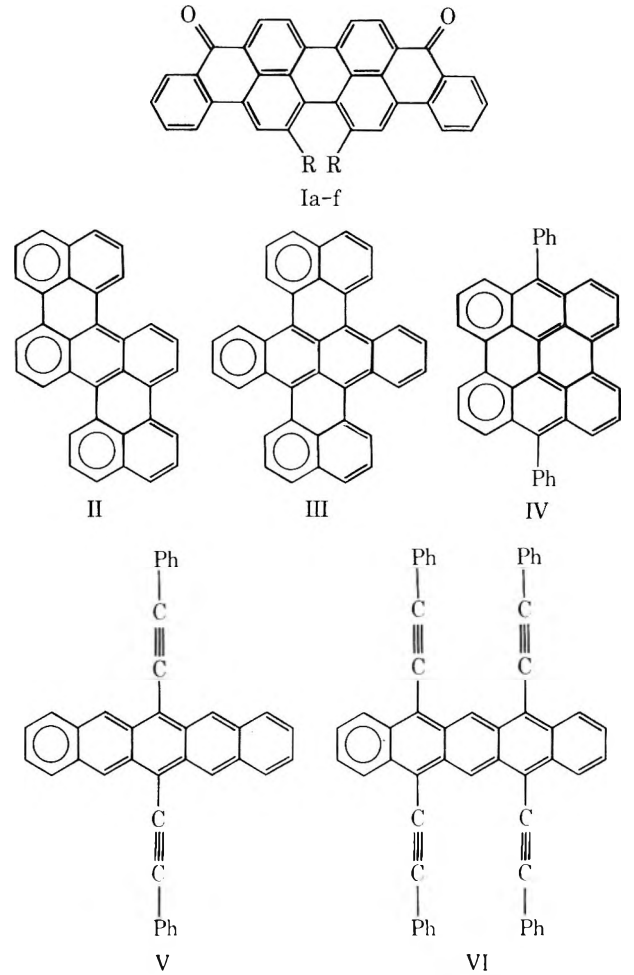
In the violanthrone series alkoxy substituents in the 16,17 positions (compounds Ib–d) provided bathochromic shifts of approximately 85 nm into the infrared, but had relatively little effect on the fluorescence quantum yield.[17] In the pentacene series substitution by two or four phenylethynyl substituents also produced substantial bathochromic shifts as has been discussed separately.[15]

For most of the compounds fluorescence quantum yields in the range of 18–51% were obtained. Solvent effects on quantum yield were noted in two cases. With IV a higher quantum yield was obtained in benzene than in ethyl benzoate or *o*-dichlorobenzene, and with Id the addition of 13% *tert*-butyl alcohol to dichlorobenzene decreased the quantum yield substantially. It is likely that the quantum yield of VI might be considerably higher in another solvent than in the 1,2,4-trichlorobenzene actually used, but the low solubility of VI prevented such measurements.

Infrared Chemiluminescence. Chemiluminescent reactions under several conditions with bis(2,4,6-trichlorophenyl) oxalate (TCPO), hydrogen peroxide, a basic catalyst, and six red or infrared fluorescers are summarized in Table II. Highest quantum yields of infrared radiation were obtained from diphenylbisanthene (IV) and from violanthrone derivatives Ib and Id. Substantially, lower quantum yields were obtained unexpectedly from the other violanthrone derivatives. There does not appear to be a straightforward correlation between either the fluorescence quantum yield or fluorescer structure and chemiluminescence quantum yield, and the variations obtained may result from decomposition of some fluorescers during the course of reaction. Two fluorescers, III and V, decomposed rapidly during chemiluminescent reactions, and reliable chemiluminescence emission data could not be obtained. The more detailed experiments with fluorescer Id indicate that higher quantum yields are obtained in ethyl benzoate than in dichlorobenzene and that quantum yields tend to decrease with increasing concentrations of TCPO.

Spectral distributions in chemiluminescence tend to be shifted toward longer wavelengths from the normal fluorescence spectra because of reabsorption of short-wavelength chemiluminescent emission by the fluorescer in the bulk solution. Self-absorption in chemiluminescence is minimized at low fluorescer concentrations, and it is evident from the comparison of chemiluminescence and fluorescence spectra in Figure 1 that singlet emission from the fluorescer is the source of chemiluminescence radiation.

Chart I
Red and Infrared Fluorescers[a]



[a] Ia (R = H), violanthrone; Ib (R = OCH_3), 16,17-dimethoxyviolanthrone; Ic (R = $OCH(CH_3)_2$), 16,17-diisopropoxyviolanthrone; Id (R = OC_6H_{13}), 16,17-dihexyloxyviolanthrone; Ie (R = OCH_2CH_2O–), 16,17-(1,2-ethylenedioxy)violanthrone; If (R = $OCOCH_3$), 16,17-diacetoxyviolanthrone; II, tetrabenzo[*de,hi,op,st*]pentacene; III, 7,8,15,16-dibenzoterrylene; IV, 4,11-diphenylbisanthene; V, 6,13-bis(phenylethynyl)pentacene; VI, 5,7,12,14-tetrakis(phenylethynyl)pentacene.

The effect of fluorescer concentration on chemiluminescence quantum yield under otherwise constant conditions is indicated by the experiments with 16,17-dihexyloxyviolanthrone (Id) in Table III. A low concentration (0.0010 *M*) of bis(2,4,6-trichlorophenyl) oxalate (TCPO) was used in the experiments to minimize possible quenching effects of TCPO and the reaction by-products on the quantum yield, and to minimize consumption of the fluorescer during the reaction. It is evident that the quantum yield increases with increasing fluorescer concentration to a limiting value. The rate of intensity decay also increases with increasing fluorescer concentration at the low concentration levels.

Discussion

Infrared fluorescence requires excited molecules having energies below 40.8 kcal mol^{-1} (>700 mμ). Since the Einstein probability for spontaneous emission of dipole radiation is proportional to the third power of the excitation en-

Table I
Absorption and Fluorescence Data

		Fluorescence data[a]				Absorbance data[e]	
		Excitation			Emission		
Fluorescer	Solvent[b]	λ_{max},[d] nm	Concn, 10^4 M	Quantum yield	λ_{max},[c] nm	λ_{max}, nm	ϵ
Ia	EB	550	5	0.35	630	607	
	DCB	550	5	0.36	637		
Ib	EB	600	7.5	0.32	713		
	DCB	600	7.5	0.29	720	658	40,340
	DCB	600	0.5	0.29	720		
Ic	EB	600	7.5	0.25	715		
	EB	600	15.0	0.27	720	648	36,630
	DCB	600	7.5	0.24	725		
	DCB	600	15.0	0.26	725		
Id	EB	600	7.5	0.29	720		
	EB	600	15.0	0.27	725		
	DCB	600	7.5	0.26	725	660	43,520
	DCB	600	15.0	0.26	725		
	DCB 87%, TBA 13%	600	10	0.14	736		
Ie	EB	600	10	0.34	680	616	
	DCB	600	7.5	0.32	680		
	DCB	600	15.0	0.34	680		
If	EB	550	5	0.67	625	582	40,800
	DCB	550	5	0.61	628		
II	Benzene	600	10	0.51	690	628	43,700[f]
	DCB	678	10	0.51	678		
III	Benzene	600	5	0.21	630, 810	750	42,200
IV	EB	600	10	0.10	730	694	30,900
	DCB	600	10	0.10	736		
	Benzene	600	5	0.18	720		
V	Benzene	600	5	0.26	680, 730	668	25,300
VI	TCB	600	5	0.08	740, 790	705	26,900

[a] Fluorescence was excited at the front surface of the sample using an excitation wavelength as indicated. [b] EB, ethylbenzoate; DCB, dichlorobenzene; TBA, *tert*-butyl alcohol; TCB, trichlorobenzene. [c] Spectral emission maxima. [d] Wavelength used for fluorescence excitation. [e] First absorption band. Absorption data obtained in *o*-dichlorobenzene, except note *f*. [f] Absorption data obtained in benzene.

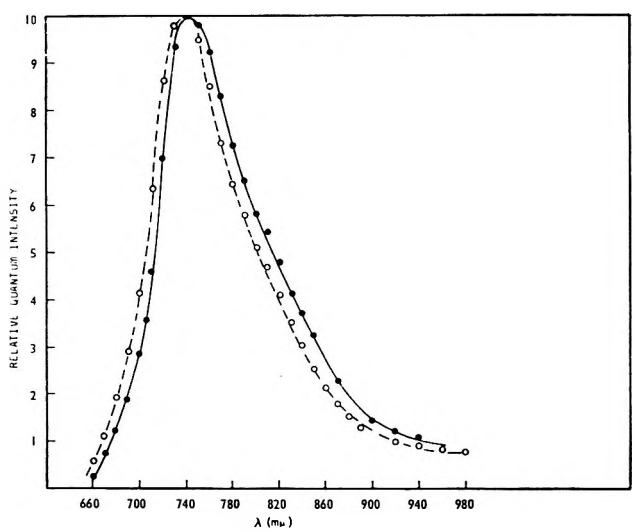


Figure 1. Id fluorescence and chemiluminescence emission. Fluorescence and chemiluminescence spectra of 16,17-dihexyloxyviolanthrone (Id) systems in 90% *o*-dichlorobenzene–10% *tert*-butyl alcohol at 25°: (○) fluorescence of 6.7×10^{-5} *M* Id; (●) chemiluminescence from reaction of 0.0010 *M* bis(2,4,6-trichlorophenyl) oxalate (TCPO), 0.010 *M* H_2O_2, 1.67×10^{-4} *M* sodium salicylate, and 6.7×10^{-5} *M* Id.

ergy, infrared fluorescers in general would be expected to have longer excited state lifetimes and lower emission efficiencies than visible fluorescers.[18] Thus, other factors being equal, fluorescent emission at 1000 nm in the infrared is 8 times less probable than green emission at 500 nm. Moreover, quenching of electronic excitation energy in internal and external vibrational modes becomes increasingly probable as the energy of the electronic transition approaches the energy of available vibrational modes.[19] Radiative efficiency losses from such internal conversion are thus more probable for infrared fluorescers than for visible fluorescers. Fluorescence theory thus indicates that the combination of low emission probability and high internal conversion probability should act to make infrared fluorescence relatively uncommon.

Available experimental data bear out these theoretical expectations; blue and green fluorescers tend to have higher quantum yields than red fluorescers even in related structural series, and red fluorescers are relatively uncommon. In spite of such considerations, however, the data in Table I show that moderately efficient fluorescence can be obtained in the 690–740 nm (41.4–38.6 kcal mol^{-1}) spectral range, although the fluorescence quantum yields are well below the values near unity available from many higher energy fluorescers.[20]

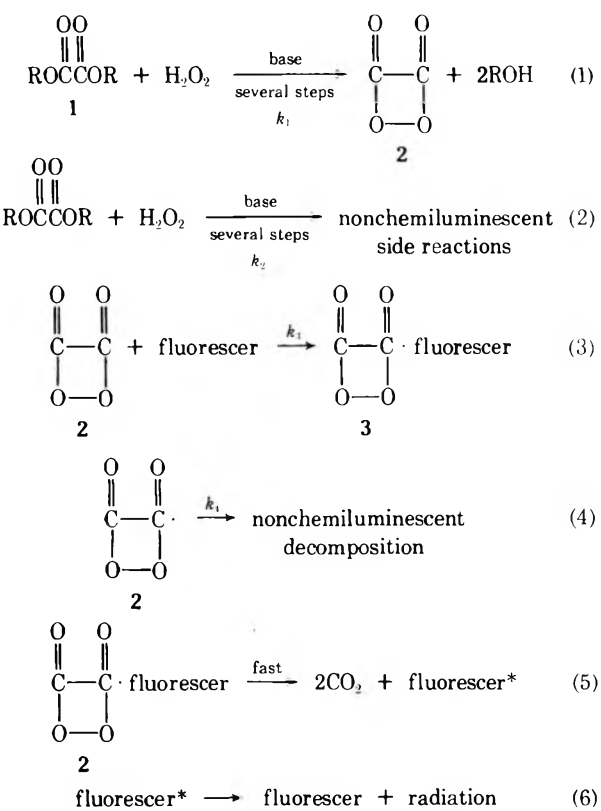
The chemiluminescence experiments (Tables II and III) combine moderately efficient infrared fluorescers with the highly efficient peroxyoxalate chemiluminescent system to produce infrared chemiluminescence quantum yields as high as 6%. Such quantum yields are high for chemiluminescent reactions in general where quantum yields well below 1% are typical,[4] but are well below quantum yields obtained with blue and yellow fluorescers in peroxyoxalate chemiluminescence.[7,8]

Table II
Infrared Chemiluminescence[a]

Fluorescer	Concn, 10^4 M	[TCPO],[b] 10^2 M	[H_2O_2], 10^2 M	[Catalyst],[c] 10^3 M	Solvent[d]	Spectral emission max, nm FL	Spectral emission max, nm CL	Quantum[e] yield, 10^2 einsteins mol^{-1}	T_f,[f] min	Max int,[g] nm ml^{-1}
IV	7.0	1.0	2.5	NaSal 1.33	DCB	736	760	2.1	5.9	168
IV	7.0	2.0	5.0	NaSal 1.33	DCB	736	760	1.2	4.2	179
If	5.0	1.0	2.5	NaSal 1.33	DCB	628	643	0.18	57	2.0
If	5.0	2.0	5.0	NaSal 1.33	DCB	628	643	0.07	20	2.7
Ie	5.0	1.0	2.5	NaSal 1.33	DCB	680	680	0.37	85	4.0
Ie	5.0	2.0	5.0	NaSal 1.33	DCB	680	680	0.10	19	4.5
Ic	7.0	1.0	2.5	NaSal 1.33	DCB	725	735	0.33	33	78
Ib	4.5	1.0	2.0	NaSal 1.33	DCB	730	740	3.1	52	
Ib	1.5	1.0	2.5	NaSal 1.33	DCB	720	740	2.8	85	37
Ib	1.5	2.0	5.0	NaSal 1.33	DCB	720	740	1.1	20	62
Id	2.2	0.5	2.5	NaSal 0.50	DCB		740	2.4	30	31
Id	4.4	1.0	2.5	NaSal 0.50	DCB	725	760	2.3	71	54
Id	10.0	1.0	2.5	NaSal 1.33	DCB	730	776	2.9	30	120
Id	10.0	2.0	5.0	NaSal 1.33	EB	725	755	3.6	16	259

[a] Reactions at 25 ± 1°. [b] TCPO, bis(2,4,6-trichlorophenyl) oxalate. [c] NaSal, sodium salicylate. [d] DCB, 90% o-dichlorobenzene–10% *tert*-butyl alcohol; EB, 90% ethyl benzoate–10% *tert*-butyl alcohol. [e] Based on TCPO. [f] Time required for emission of three-quarters of the total radiation. [g] Maximum intensity in microwatts per milliliter of reaction mixture.

Mechanistic Significance and the Yield of the Key Intermediate. The mechanism proposed for oxalic ester chemiluminescence[8] involves the following essential steps (eq 1–6). According to this mechanism the chemiluminescence quantum yield (Q) will be the product of (a) the yield of key intermediate **2** from oxalate ester **1** (Y_{ki}) in competing steps 1 and 2, (b) the yield of complex **3** from **2** (Y_{cT}) in competing steps 3 and 4, (c) the yield of excited fluorescer from decomposition of **3** in step 5 (Y_{ex}), and (d) the fluorescence yield of the fluorescer in step 6 (Y_{fl}):



$$Q = Y_{ki}Y_{cT}Y_{ex}Y_{fl}$$

The yield of complex (Y_{cT}) from competive steps 3 and 4, provided the fluorescer concentration is constant during an experiment, will be

$$Y_{cT} = \frac{k_3[\mathrm{FLR}]}{k_3[\mathrm{FLR}] + k_4}$$

Thus the quantum yield, Q, in experiments carried out at constant fluorescer concentration will be

$$Q = Y_{ki}Y_{ex}Y_{fl}\frac{k_3[\mathrm{FLR}]}{k_3[\mathrm{FLR}] + k_4}$$

Inverting this equation one obtains

$$1/Q = \frac{1}{Y_{ki}Y_{ex}Y_{fl}} + \frac{1}{Y_{ki}Y_{ex}Y_{fl}}\frac{k_4}{k_3}\frac{1}{[\mathrm{FLR}]}$$

The mechanism thus predicts that under constant reaction conditions where Y_{ki}, Y_{ex}, and Y_{fl} are constant, a plot of the reciprocal of the quantum yield *vs.* the reciprocal of the fluorescer concentration will give a straight line with an intercept of $1/Y_{ki}Y_{ex}Y_{fl}$, and a slope of $(1/Y_{ki}Y_{ex}Y_{fl})(k_4/k_3)$. The ratio k_3/k_4 is then available as the quotient of intercept/slope.

Table III
Effect of 16,17-Dihexyloxyviolantrone (Id) Concentration on Chemiluminescence Quantum Yield and Reaction Rate[a]

[Id], 10^4 M	Quantum yield, 10^2 einsteins mol^{-1}	Emission[b] lifetime, min
0.67	2.16	40
1.67	3.50	21
3.33	4.58	21
6.67	6.02	16
10.00	5.94	17

[a] Reactions of 0.001 *M* bis(2,4,6-trichlorophenyl) oxalate, 0.01 *M* H_2O_2, and 1.67×10^{-4} *M* sodium salicylate in 87% o-dichlorobenzene–13% *tert*-butyl alcohol at 25 ± 1°. [b] Time required for emission of 75% of the total radiation output.

A plot of $1/Q$ *vs.* 1/[FLR] for the data of Table III is shown in Figure 2. A satisfactory straight line is obtained having an intercept of 14.5 and a slope of 2.2×10^{-3}. The quantum yield for the reaction at infinite fluorescer con-

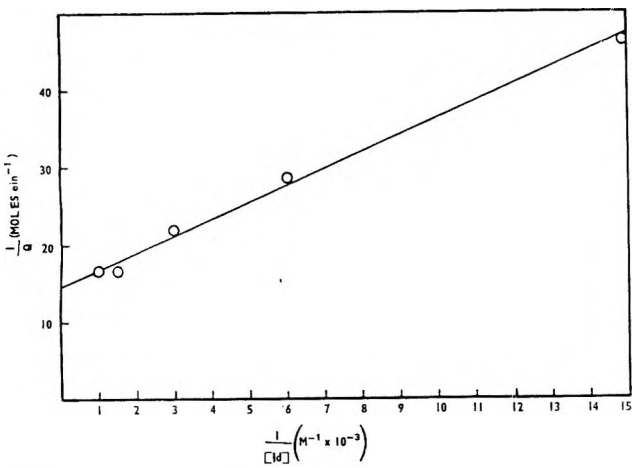


Figure 2. Relationship of chemiluminescence quantum yield, Q, to fluorescer (Id) concentration. Data from Table III.

centration is the reciprocal of the intercept or 0.069 einstein mol^{-1}. Since the fluorescence quantum yield under the reaction conditions is 0.14, the yield of excited fluorescer based on the concentration of TCPO is 0.069/0.14 or 49%. Since the yield of excited fluorescer in step 5 cannot be greater than unity, the yield of 2 must also be at least 49% under the reaction conditions employed in the experiments.

The rate ratio k_3/k_4 obtained from the quotient of intercept/slope is 6.6×10^3. This high value confirms earlier experiments which indicated that the fluorescer acts as a catalyst for the decomposition of key intermediate 2.[8]

Although the time required for the emission of three-quarters of the total radiation is not an accurate measure of the reaction rate, the increase in rate of intensity decay with increasing fluorescer concentration between 0.67×10^{-4} and 1.67×10^{-4} M suggests that step 3 may in part be rate determining at very low fluorescer concentrations. The similar decay rates obtained at fluorescer concentrations of 1.67×10^{-4} M and higher, however, indicates that step 3 is fast relative to step 1 when sufficient fluorescer is present.

Experimental Section

Materials. *o*-Dichlorobenzene (Eastman) and *tert*-butyl alcohol (Eastman) were fractionally distilled; reagent 98% hydrogen peroxide was obtained from BeccoChemical Division, FMC Co. The 16,17-disubstituted violanthrones, dihydroxy- and dimethoxy-Ib, diisoproxy-Ic, ethylenedioxy-Ie, and diacetoxy-If were obtained from the Organic Chemical Division, American Cyanamid Compound, Bound Brook, N.J. The high melting compounds Ib and Ie were purified by extraction in a Soxhlet thimble with pyridine; the diisopoxy derivative Ic, mp 342°, was purified by chromatography on alumina with pyridine–ethyl acetate; recrystallization of If from pyridine gave crystals, mp 300°. Hydrocarbons II,[21] V,[15] and VI[15] were prepared by methods previously described. Iodine-catalyzed photocyclization of 10,10′-diphenyl[$\Delta^{9,9'(10H,10'H)}$-bianthracene]-10,10′-diol afforded 4,11-diphenylbisanthene (IV).[22] Bis(2,4,6-trichlorophenyl) oxalate, mp 190.5–192.5°, was prepared as previously described.[8]

16,17-Dihexyloxyviolanthrone (Id). To a mixture of 76.7 g (0.16 mol) of 16,17-dihydroxyviolanthrone and 153.5 g of potassium carbonate in 400 ml of 1,2,4-trichlorobenzene heated to 120° was added during 3 hr 133 g (0.81 mol) of *n*-hexyl bromide. The mixture was heated at 120–130° for another 8 hr, cooled, and poured into 1.5 l. of water. The solid was separated and washed with 1200 ml of refluxing methanol. An absorption spectrum indicated that the 46.2 g of product was 80% pure. Recrystallization from benzene gave dark maroon crystals, mp 242–243°.

Anal. Calcd for $C_{46}H_{40}O_4$: C, 84.12; H, 6.14. Found: C, 84.06; H, 6.22.

5,12-Dihydroxy-5,12-dinaphthyl-5,12-dihydronaphthacene. A modification of an earlier method[23] gave a diol which had a substantially higher melting point than reported. To 1-naphthyllithium, prepared from 8.69 g (0.042 mol) of 1-bromonaphthalene and 0.56 g (0.08 g-atom) of lithium in 30 ml of anhydrous ethyl ether, was added 2.58 g (0.01 mol) of 5,12-naphthacenequinone[24] and 70 ml of anhydrous benzene. The mixture was refluxd for 2 hr, then decomposed by the addition of 25 ml of ethanol. Dilution with water gave a solid which was recrystallized from xylene. The yield of the colorless product, mp 297–299° (lit.[23] mp 242°), was 3.75 g (73%); mass spectrum had *m/e* 514, 512, 496, 480, and 370. The single peak at 3572 cm^{-1} ($CHCl_3$) established the trans reationship of the two hydroxy groups.

Anal. Calcd for $C_{38}H_{26}O_2$: C, 88.72; H, 5.05. Found: C, 88.56; H, 5.36.

7,8,15,16-Dibenzoterrylene (III). A previously described[23] cyclization of 5,12-dihydroxy-5,12-dinaphthyl-5,12-dihydronaphthacene was followed to obtain III. The crude material was chromatographed on silica gel with 1,2,4-trichlorobenzene to obtain 12% of III as a green solid, mp 360°; mass spectrum *m/e* 476.

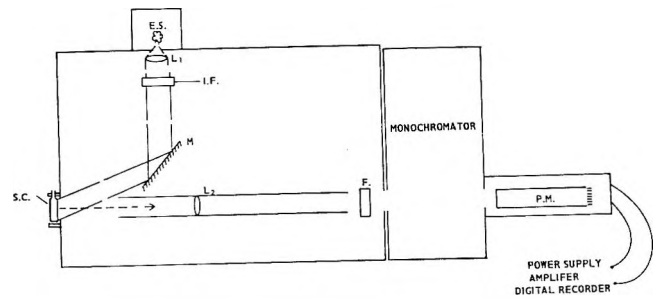


Figure 3. Diagram of spectroradiometer: S.C., sample cell; E.S., excitation source; L_1 + L_2, focusing lens; I.F., interference filter; F., blocking filter; P.M., photomultiplier.

Instrumentation. Description. A diagram outlining the essential features of the spectroradiometer is shown in Figure 3. The excitation source was a Quartz-Iodine, 40-W tungsten lamp mounted vertically inside a housing equipped with a collimating glass lens. Provision was made to insert 2-in.-square interference filters into the excitation beam to isolate appropriate wavelength regions. The sample cuvette (1 cm thick, 22 mm diameter) and collimetor lens (1.5 in. diameter, 10 cm focal length) were positioned 40 and 20 cm, respectively, from the monochromotor entrance slit. A blackened aluminum tube served as a lens holder and light baffle, to reduce stray light. The monochromotor was a Jarrell-Ash 0.25-m Ebert type with fixed 1-mm interchangeable slits and incorporated two gratings blazed at 0.6 and 1.2 μ. The S-1 response detector was a Fairchild-Dumont No. 6911 photomultiplier mounted inside a cooled Electro Optics Associates housing assembly No. P.M. 101. A Fluke Model 412B and a Keithley Model 414 were used as photomultiplier power supply and amplifier, respectively. The photomultiplier was operated at −78° through Dry Ice cooling. Operating the photomultiplier at 1000 V and the amplifier at 10^{-8} A produced excellent linearity and reproducibility.

Data (amplifier output) were recorded digitally on a United Systems DIGITEC Assembly consisting of a Model 201-N digital voltmeter, Model 661 digital clock, and a Model 611/620 printer system. Printed, paper tape data were then processed by an S.D.S. 930 computer programmed with the calibration data.

Calibration. Relative calibration was obtained using a National Bureau of Standards lamp; absolute calibration was made by reference to an absolute Roberts-Hirt spectroradiometer.[25]

Light Measurements. Fluorescence and chemiluminescence experiments were carried out as previously described.[8]

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Registry No.—Ia, 116-71-2; Ib, 128-58-5; Ic, 53418-57-8; Id, 53418-58-9; Ie, 6424-76-6; If, 53418-59-0; I (R = OH), 128-59-6; II, 191-79-7; III, 187-96-2; IV, 23102-66-1; V, 18826-31-8; VI, 18826-38-5; 10,10′-diphenyl[$\Delta^{9,9'(10H,10H)}$-bianthracene]-10,10′-diol, 53418-60-3; *n*-hexyl bromide, 111-25-1; 5,12-dihydroxy-5,2-dinaphthyl-5,12-dihydronaphthacene, 53418-61-4; 1-bromonaph-

thalene, 90-11-9; 5,12-naphthacenequinone, 1090-13-7; bis(2,4,6-trichlorophenyl) oxalate, 1165-91-9.

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Stereochemistry of the Exchange Reaction between Lithium Tetrachloropalladate and Alkylmercury Compounds

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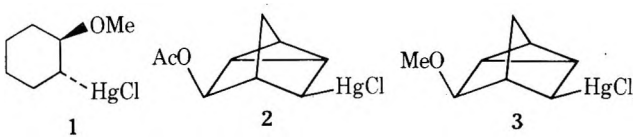
The carbomethoxylation of several σ-bonded organomercurials (derived from the oxymercuration of cyclohexene and norbornadiene) in the presence of stoichiometric amounts of lithium tetrachloropalladate and carbon monoxide was found to proceed with predominant retention of configuration at carbon. Since the carbomethoxylation of alkylpalladium compounds occurs with complete retention of configuration at carbon, therefore the exchange of palladium for mercury occurs with predominant retention of configuration.

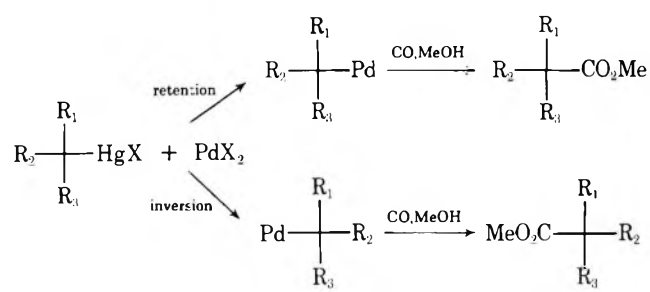
The organometallic exchange reaction is a generally employed method for the generation of transition metal–carbon σ bonds[1] and the formation of σ-bonded organopalladium complexes *via* palladium exchange with organomercurials has been used extensively in the arylation, methylation, and carbomethoxylation of olefins.[2-5] Alkylmercury compounds of known configuration can be readily obtained *via* the solvomercuration of olefins and the stereochemistry of addition to simple olefins is trans.[6] The exchange of palladium for mercury is, therefore, a possible method of stereospecifically synthesizing palladium–carbon σ-bonded complexes. The stereochemistry of the exchange process can be determined by trapping the unstable alkylpalladium intermediate with carbon monoxide in methanol[5] since the conversion of alkylpalladium complexes to esters has been shown to proceed with complete retention of configuration at the carbon bearing the metal.[7] Structural analysis of the methyl ester formed would establish the stereochemistry of the exchange reaction. (See Scheme I.)

Thus, the carbonylation of alkylmercury compounds **1**,[8] **2**,[9] and **3**,[10] in the presence of lithium tetrachloropalladate



1 2 3

Scheme I

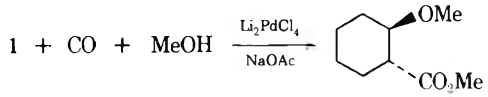


in methanol was investigated to determine the stereochemistry of the exchange process.

Results and Discussion

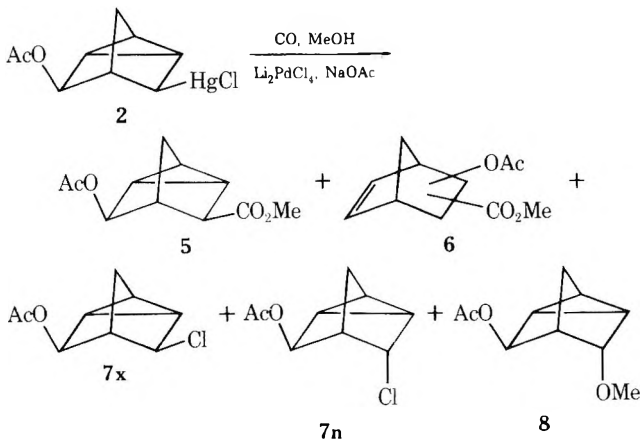
The carbonylation of *trans*-2-methoxycyclohexylmercuric chloride (**1**) in methanol in the presence of sodium acetate was effected by treatment of **1** with lithium tetrachloropalladate and carbon monoxide (1 atm) at room temperature. The reaction afforded methyl *trans*-2-methoxycyclohexylcarboxylate (**4**)[5] in a 7% yield. No attempts were made to isolate low-boiling organic products which were removed during the work-up. The low yield of **4** suggests the carbonylation did not compete favorably with the decom-

position of the unstable organopalladium intermediate *via* β-palladium hydride elimination.



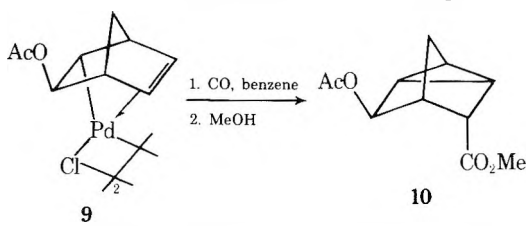
4

Carbonylation of *exo,exo*-3-acetoxynortricyclyl-5-mercuric chloride (**2**) gave a product mixture consisting of 64% *exo,exo*-3-acetoxy-5-carbomethoxynortricyclene (**5**), 8% acetoxycarbomethoxynorbornene (**6**), 14% *exo,exo*-3-acetoxy-5-chloronortricyclene (**7x**), 7% *exo,endo*-3-acetoxy-5-chloronortricyclene (**7n**), and 6% *exo,endo*-3-acetoxy-5-methoxynortricyclene (**8**) in a total yield of 61%.



2 5 6 7x 7n 8

The exo,exo geometry at the 3 and 5 positions of **5** was assigned on the basis of chemical shift data. It has been well documented that in 3,5-disubstituted nortricyclenes, endo substitution at the 5 position produces a paramagnetic shift of the 3-endo proton, whereas exo substituents at the 5 position have negligible effect on the chemical shift of the 3-endo proton.[7,9,11] The chemical shift value of the C_3 methine proton (δ 4.65) of **5** was almost identical with that of the corresponding proton of **7x**[9] (δ 4.62), but upfield of the C_3 methine proton resonance (δ 4.93) of *exo,endo*-3-acetoxy-5-carbomethoxynortricyclene (**10**) owing to the "nearest-neighbor" deshielding effect. The endo methyl ester **10** was independently synthesized by the carbonylation of the σ-bonded palladium complex **9** obtained from treatment of dichloro(norbornadiene)palladium(II) with silver acetate. A number of structural investigations have

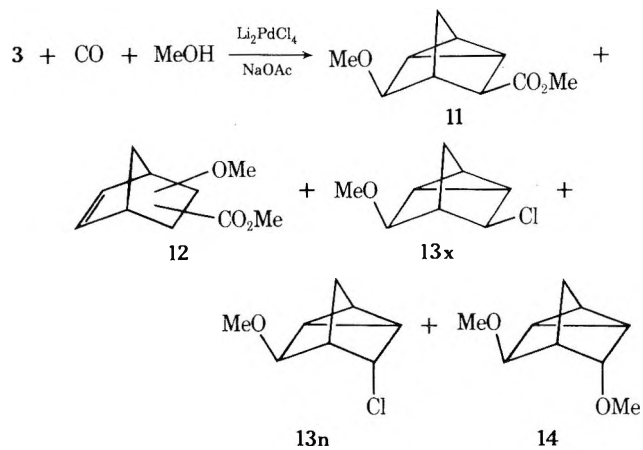


9 10

established that oxypalladation of palladium(II)–diolefin complexes proceeds trans with the oxo group exo and the metal endo or inside in each case.[12-15] The structure **10** was established on the basis that the analogous methoxyenyl complex underwent carbonylation to afford *exo,endo*-3-methoxy-5-carbomethoxynortricyclene.[7]

Nmr and mass spectral analyses showed that **6** had the gross structure shown; however, the positions of the acetoxy and carbomethoxy substituents could not be elucidated. The nortricyclyl chlorides **7x** and **7n** were identified by nmr and vpc comparison with authentic samples.[9] The nmr spectrum of **8** was in good agreement with the assigned exo,endo structure; the signal for the proton on the carbon bearing the acetoxy group (δ 5.13) was downfield from the corresponding proton resonances in **5** and **7x** (δ 4.65 and 4.62, respectively) due to the deshielding of the endo methoxy group.

The carbonylation of *exo,exo*-3-methoxynortricyclyl-5-mercuric chloride (**3**) afforded a 41% yield of a product mixture consisting of 34% *exo,exo*-3-methoxy-5-carbomethoxynortricyclene (**11**), 10% methoxycarbomethoxynorbornene (**12**), 31% *exo,exo*-3-methoxy-5-chloronortricyclene (**13x**), 18% *exo,endo*-3-methoxy-5-chloronortricyclene (**13n**), and 5% *exo,endo*-3,5-dimethoxynortricyclene (**14**).



11 12 13x 13n 14

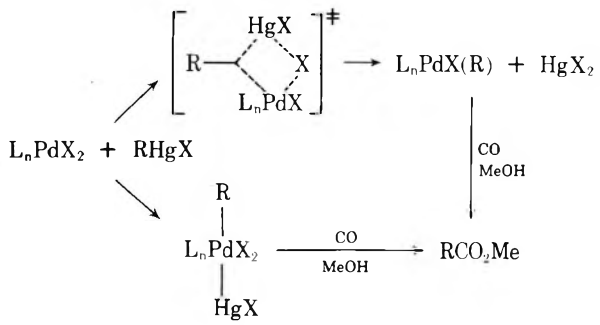
Identification of the ester **11** and the chlorides **13x**[16] and **13n**[11] was made by vpc and nmr comparison with authentic samples. The exo,endo stereochemistry of the diether **14** was inferred from nmr chemical shift data which showed that the absorption for the proton on the carbon bearing the exo methoxy group (δ 3.97) was shifted downfield relative to the corresponding proton signal (δ 3.32) of *exo,exo*-3,5-dimethoxynortricyclene.[16] The norbornene skeleton for **12** was established by nmr analysis, although the positions of the methoxy and carbomethoxy substituents could not be elucidated.

The absence of endo nortricyclyl methyl esters from **2** and **3** suggests that the palladium–mercury exchange process does not involve intermediate carbon-free radicals. The reduction of **2** by sodium borohydride has been shown to proceed *via* radical intermediates.[17] When the reduction was carried out with sodium borodeuteride, deuterium was shown to be incorporated about equally among the 5-exo and 5-endo positions of 3-acetoxynortricyclene.[17]

The predominant retention of configuration at carbon during the carbomethoxylation of **1**, **2**, and **3** is consistent with either a four-center[18] bimolecular electrophilic exchange of palladium for mercury or an oxidative addition of organomercury compounds to a palladium(II) species with retention of configuration at carbon. The oxidative addition of an organomercury compound to a d^8 transition metal complex to form a bimetallic complex containing a carbon–transition metal σ bond has been observed in fact, for a d^8 rhodium complex.[19]

The stereospecific formation of **4** could be the consequence of factors extraneous to the reaction mechanism. Although an interaction between palladium and methoxy could favor the formation of a *trans*-methoxycyclohexylpalladate intermediate (which upon carbonylation would form the trans ester **4**), an ether oxygen is a poor nucleophile. Extraneous electronic and steric effects are unlikely to be responsible for the formation of the exo esters **5** and **11**. The "endo protection" often observed in the norbornyl system does not exist here since the nortricyclene skeleton possesses C_{3v} symmetry. (See Scheme II.)

Scheme II



The rearranged esters **6** and **12** could arise from three possible pathways as illustrated for **2** in Scheme III. Path A involves an initial exchange of palladium for mercury with retention of configuration followed by the rearrangement of the intermediate alkylpalladium complex in a manner reminiscent of the interconversion of cyclopropylmethyl and 3-buten-1-yl Grignard reagents.[20] The rearrangement may be regarded formally as a cis β elimination of a palladium alkyl to give the norbornenylpalladium intermediate **15.** Subsequent carbomethoxylation with retention of configuration at carbon[7] would afford *endo,syn*-2-carbomethoxy-7-acetoxynorborn-5-ene (**6a**) as the rearranged ester. Alternatively, the exchange of palladium for mercury may proceed partially with inversion of configuration to afford a nortricyclylpalladium intermediate which rearranges to the norbornenylpalladium complex **16** (path B). Replacement of palladium with the carbomethoxy group with retention of configuration would give *exo,endo*-2-acetoxy-3-carbomethoxynorborn-5-ene (**6b**) as the rearranged ester. In path C, a palladium species inserts into a cyclopropane carbon–carbon single bond *via* oxidative addition to give an unstable palladium(IV) intermediate which decomposes to the norbornenylpalladium(II) complex **16.** Subsequent carbomethoxylation would afford **6b** as the rearranged ester. Insertion of d^8 complexes of platinum and rhodium into cyclopropane rings has been observed.[21]

Nmr double resonance results are compatible with the structure **6a.** In the nmr spectrum of **6,** a doublet of doublets (J = 12.5 Hz, 4.0 Hz) centered at δ 1.54 and a doublet of multiplets (J = 12.5 Hz) centered at δ ~2.0 may be assigned to the two methylene protons H_C and H_B of **6a,** respectively, on the basis of their relative chemical shifts[22] (Figure 1). Irradiation of H_D (δ 3.15) removed the 4-Hz splitting of the H_C signal. The value of 4.0 Hz for J_{CD} is in agreement with trans endo–exo coupling constants observed for systems of similar structure.[23,24] Since vicinal coupling constants between the bridgehead protons and the C_7 bridge protons in norbornene systems are in the range of 0–2 Hz[23,24] and no coupling exists between the C_2 exo proton and the C_7 bridge protons, the structure **6b** is therefore incompatible with the double-irradiation results.

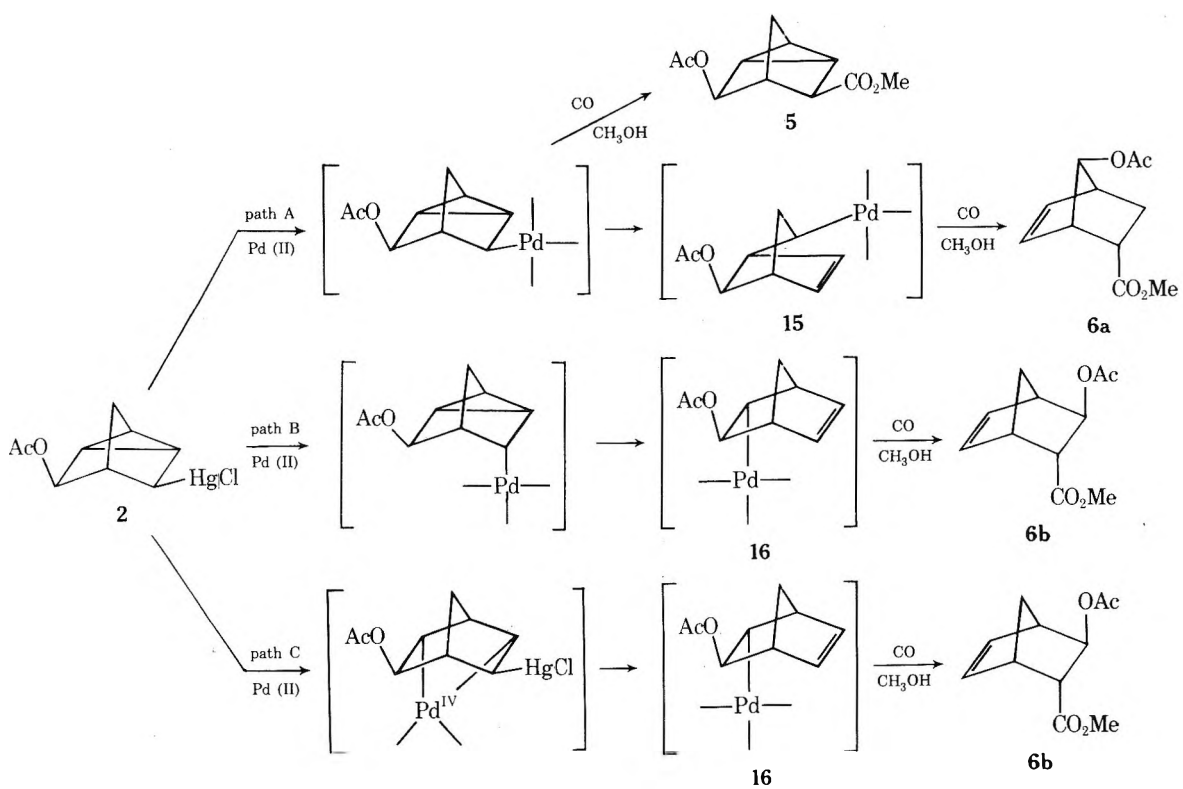
Increasing the carbon monoxide pressure (3 atm) in the carbonylation of **3** reduced the formation of the rearranged ester **12** to a trace amount. This observation is consistent with path A in which the nortricyclylpalladium intermediate can either undergo carbonylation to afford **11** or rearrange to a norbornenylpalladium complex to yield **12.** Increasing the carbon monoxide pressure increases the rate at which the nortricyclylpalladium complex is trapped, thus suppressing the formation of the rearranged ester **12.** Neither path B nor path C would exhibit such a carbon monoxide pressure effect on the rearrangement.

The nonester products were most likely obtained from the decomposition of and nucleophilic displacements on the intermediate alkylpalladium complexes.

Experimental Section

Preparation of Di-μ-chloro-bis(6-acetoxybicyclo-[2.2.1]hept-2-ene-*endo*-5σ,2π)dipalladium(II) (9). The preparation of this compound was carried out using a procedure similar to that described for the acetoxylation of dichloro(1,5-cyclooctadiene)palladium.[25] A mixture of 1.0 g (3.8 mmol) of dichloro(norbornadiene)palladium(II)[26] and 0.64 g (3.8 mmol) of silver acetate

Scheme III



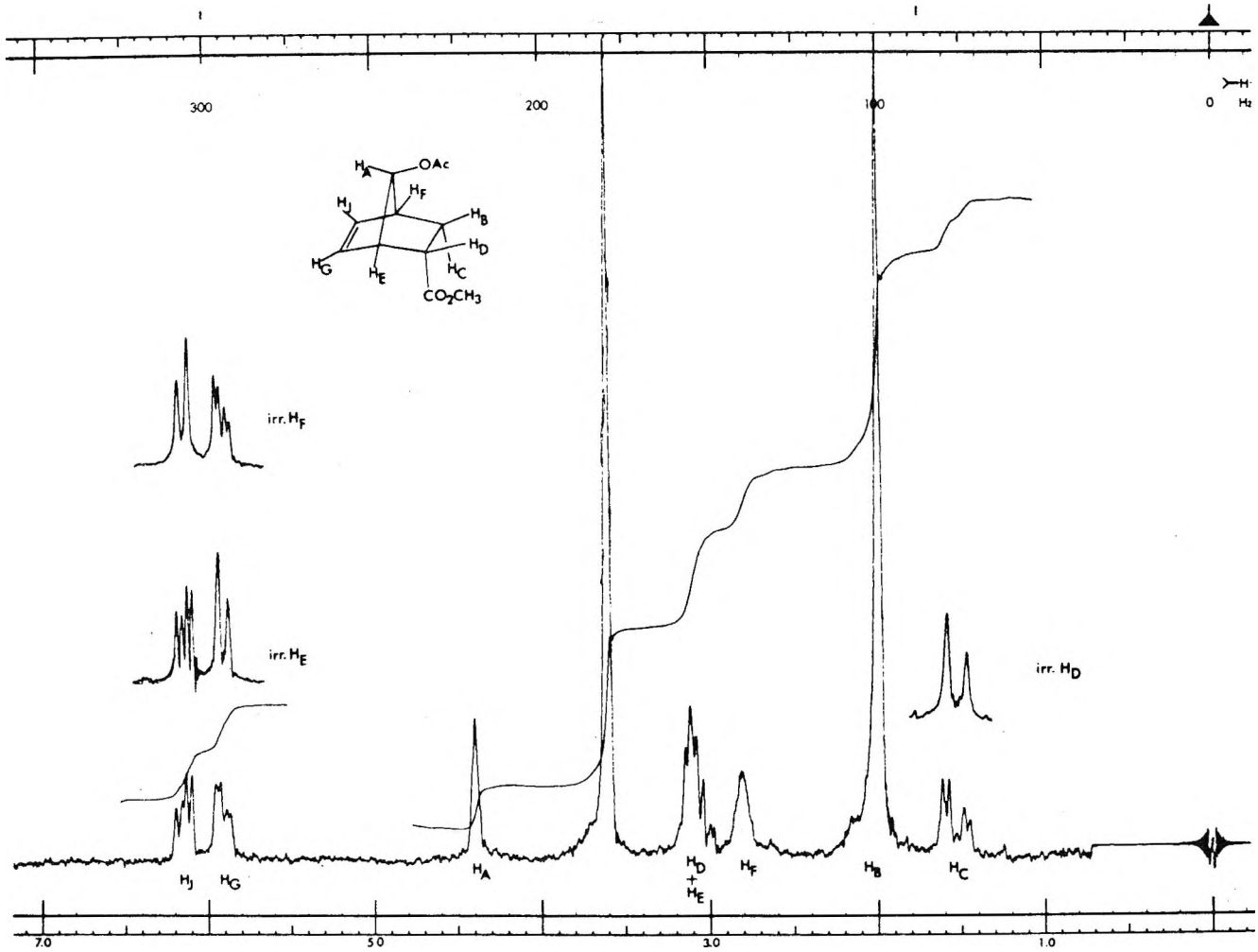


Figure 1.

in 200 ml of chloroform was stirred at room temperature for 1 hr. The silver salt was removed and the filtrate was concentrated under reduced pressure. The residue was triturated with ether and the resulting cream-colored complex was collected by gravity filtration to afford 0.7 g (1.2 mmol, 63%) of **9**. *Anal.* Calcd for $C_9H_{11}ClO_2Pd$: C, 36.86; H, 3.75. Found: C, 35.52; H, 3.63.

Carbonylation of Di-μ-chloro-bis(6-acetoxybicyclo-[2.2.1]hept-2-ene-*endo*-5σ,2π)dipalladium(II) (9). Formation of *exo,endo*-3-Acetoxy-5-carbomethoxynortricyclene (10). A mixture of 0.5 g (0.85 mmol) of **9** and 0.5 g (6.1 mmol) of sodium acetate in 120 ml of benzene was stirred under an atmosphere of carbon monoxide at room temperature for 3 hr. To the resulting mixture was added 50 ml of methanol. After 8 hr at room temperature, the reaction mixture was filtered gravimetrically to remove palladium metal. The filtrate was concentrated under reduced pressure and the residue was extracted with several small portions of ether. The combined ether extracts were washed with aqueous sodium bicarbonate and dried over magnesium sulfate. Removal of ether under reduced pressure gave 0.23 g of an oil which was purified by preparative vpc using a 10 ft × ⅜ in. 20% DEGS/Chromosorb W column to afford **10:** nmr ($CDCl_3$) δ 4.93 (t, 1, AcOC*H*), 3.69 (s, 3, OCH_3), 2.51 (t, 1, CH_3O_2CCH), 2.31 (bs, 1), 2.02 (s, 3, CH_3CO_2), 1.90 (m, 1), and 1.3–1.7 ppm (4); mass spectrum (70 eV) *m/e* 210 (M^+).

Carbonylation of *trans*-2-Methoxycyclohexylmercuric Chloride (1). To a mixture of 3.57 g (10 mmol) of **1**[8] and 2.0 g (24.4 mmol) of sodium acetate in 30 ml of methanol was added a solution of 1.77 g (10 mmol) of palladium chloride and 0.85 g (20 mmol) of lithium chloride in 100 ml of methanol under an atmosphere of carbon monoxide. The reaction mixture was stirred at room temperature under carbon monoxide for 10 hr and then filtered gravimetrically to remove the precipitated metal and salts. The colorless filtrate was concentrated under reduced pressure and the residue was extracted with several small portions of pentane. The combined pentane extracts were washed with aqueous sodium bicarbonate and dried over magnesium sulfate. Removal of pentane under reduced pressure afforded 0.13 g (0.7 mmol, 7%) of a liquid which was identified as methyl *trans*-2-methoxycyclohexylcarboxylate (**4**)[5] by vpc and nmr comparison with an authentic sample: nmr ($CDCl_3$) δ 3.68 (s, 3, CO_2CH_3), 3.42 (s, 3, OCH_3), 3.42 (m, 1, CH_3OCH), and 2.7–0.8 ppm (9).

Carbonylation of *exo,exo*-3-Acetoxynortricyclyl-5-mercuric Chloride (2). The carbonylation of a mixture of 4.37 g (11.28 mmol) of **2**,[9] 2.0 g (11.28 mmol) of palladium chloride, 1.0 g (23.6 mmol) of lithium chloride, 2.0 g (24.4 mmol) of sodium acetate, and 150 ml of methanol was effected in a manner described above to afford 1.4 g of organic products consisting of five components. The products were separated by vpc using a 20 ft × ⅜ in. 30% DEGS/Chromosorb W column. Two of the minor components were identified as *exo,exo*-3-acetoxy-5-chloronortricyclene (**7x**) (14%) and *exo,endo*-3-acetoxy-5-chloronortricyclene (**7n**) (7%), respectively, by nmr comparison with authentic samples.[9] A third nonester product was assigned the structure *exo,endo*-3-acetoxy-5-methoxynortricyclene (**8**) (6%): nmr ($CDCl_3$) δ 5.13 (t, 1, AcOCH), 3.53 (t, 1, CH_3OCH), 3.30 (s, 3, OCH_3), 2.03 (s, 3, O_2CCH_3), and 2.4–1.3 ppm (6); mass spectrum (70 eV) *m/e* 182 (M^+). The major ester product was identified as *exo,exo*-3-acetoxy-5-carbomethoxynortricyclene (**5**) (64%): mp 33–34°; nmr ($CDCl_3$) δ 4.65 (t, 1, AcOCH), 3.65 (s, 3, CO_2CH_3), 2.56 (bs, 1, $HCCO_2CH_3$), 2.38 (bs, 1), 2.02 (s, 3, O_2CCH_3), and 1.9–1.3 ppm (5); mass spectrum (70 eV) *m/e* 210 (M^+). The minor ester product was identified as acetoxycarbomethoxynorbornene (**6**) (8%): nmr ($CDCl_3$) δ 6.26 (dd, 1, J = 6 Hz, 3.8 Hz), 5.92 (dd, 1, J = 6 Hz, 3 Hz), 4.41 (m, 1, AcOCH), 3.54 (s, 3, CO_2CH_3), 3.11 (m, 2), 2.81 (m, 2), 2.03 (s, 3, O_2CCH_3), 2.0 (m, 1), and 1.54 ppm (dd, 1, J = 12.5 Hz, 4 Hz); mass spectrum (70 eV) *m/e* 210 (M^+).

Carbonylation of *exo,exo*-3-Methoxynortricyclyl-5-mercuric Chloride (3). Carbonylation of a mixture of 2.0 g (5.6 mmol) of **3**,[10] 1.0 g (5.64 mmol) of palladium chloride, 0.5 g (11.8 mmol) of lithium chloride, and 1.0 g of sodium acetate in 100 ml of methanol in the manner described above afforded 0.7 g of organic products consisting of five components which were separated by preparative vpc using a 20 ft × ⅜ in. 30% DEGS/Chromosorb W column. Two of the components were identified as *exo,exo*-3-methoxy-5-

chloronortricyclene (**13x**) (31%) and *exo,endo*-3-methoxy-5-chloronortricyclene (**13n**) (18%), respectively, by nmr comparison with authentic samples.[16] A third nonester product was assigned the structure *exo,endo*-3,5-dimethoxynortricyclene (**14**) (5%): nmr ($CDCl_3$) δ 3.97 (bs, 1), 3.52 (t, 1), 3.30 (s, 6), and 2.2–1.2 ppm (6); mass spectrum (70 eV) *m/e* 154 (M^+). The major ester product was indentified as *exo,exo*-3-methoxy-5-carbomethoxynortricyclene (**11**) (34%) by vpc and nmr comparison with an authentic sample.[7] The minor ester product was identified as methoxycarbomethoxynortricyclene (**12**) (10%): nmr ($CDCl_3$) δ 6.10 (dd, 1, J = 6.1 Hz, 3.8 Hz), 5.88 (dd, 1, J = 6.1 Hz, 3.0 Hz), 3.62 (s, 3) 3.25 (s, 3), 3.3–2.6 (4), 1.87 (dm, 1, J = 12.5 Hz), and 1.44 ppm (dd, 1, J = 12.5 Hz, 3.8 Hz); mass spectrum (70 eV) *m/e* 183 (M^+).

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A Stereochemical Study of the Mechanism of the Conversion of Phenyl(trichloromethyl)carbinol to α-Methoxyphenylacetic Acid[1]

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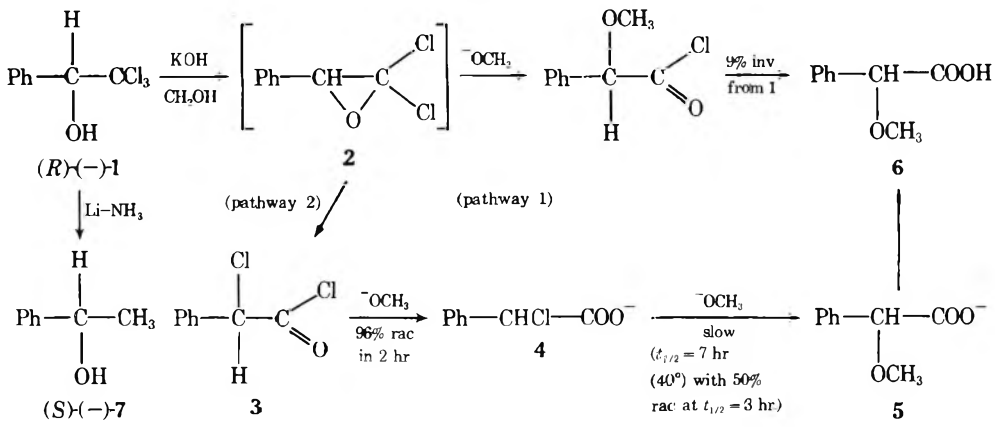
Two reaction pathways are considered for the reaction of phenyl(trichloromethyl)carbinol (1) with sodium methoxide to α-methoxyphenylacetic acid in methanol. Pathway 1 involves the conversion of the carbinol to a dichloro epoxide (2), followed by an SN2 attack of the methoxide nucleophile to give α-methoxyphenylacetic acid; this pathway involves one stereochemical inversion. The second pathway involves initial formation of the dichloro epoxide 2 followed by an intramolecular rearrangement to α-chlorophenylacetate anion and a subsequent attack of the methoxide nucleophile on this anion. This second pathway involves almost complete racemization during the 2-hr reaction period used; one step alone (3 going to 4) involves 96% racemization, and, in the next step, racemization of 4 occurs twice as fast as the conversion of 4 to 5. The second pathway is proven to account for the formation of approximately 23% of the final product by the detection of the presence of 20% α-chlorophenylacetic acid in the crude α-methoxyphenylacetic acid and by measuring the kinetics of the reaction of the α-chloro acid with methoxide anion. The balance of the reaction proceeds by pathway 1 and this reaction pathway accounts for the stereochemistry experimentally observed. Nine per cent inversion of configuration occurs with the balance racemization. Control experiments show that the large amount of racemization is due to the ease with which α-methoxyphenylacetate anion racemizes in the methanolic potassium hydroxide reaction medium.

Phenyl(trichloromethyl)carbinol (1) reacts with a wide variety of nucleophiles at 50° in methanolic potassium hydroxide to form α-substituted phenylacetyl chlorides. These are not isolated but usually react with the basic solution to form α-substituted phenylacetate anions. Examples include reaction of the carbinol with methoxide to give α-methoxyphenylacetic acid[2] and with potassium amide in liquid ammonia to form α-aminophenylacetic acid.[3] With some nucleophiles ring closure occurs; thiourea forms 2-imino-5-phenyl-4-thiazolidinone,[4] and cyanamide forms alkyl 5-aryl-2-imino-4-oxo-1-imidazolidinecarboximidates.[5] All of these reactions occur in yields of 45–80% of the theoretical.

These reactions have been postulated to proceed through a dichloro epoxide (2) followed by an SN2 attack of the nucleophile on this epoxide. This seems inherently reasonable because it is necessary to rationalize somehow the facile substitution of the α-hydroxyl group of the starting carbinol by the new nucleophile, and it is well-known that hydroxyl groups themselves are very poor leaving groups in SN2 reactions. The hydroxyl group of phenyl(trichloromethyl)carbinol is even more inert than the hydroxyl group of a typical secondary alcohol; it does not react with Lucas reagent (concentrated hydrochloric acid containing zinc chloride), either under the usual room-temperature conditions or after standing at steam bath temperature for 90 min.

An alternative mechanism involves the dichloro epoxide intermediate first rearranging to the α-chlorophenylacetyl chloride, which then hydrolyzes and reacts with the nucleophile. Phenyl(trichloromethyl)carbinol is known to be slowly converted to α-chlorophenylacetic acid in 27% yield by 10% aqueous potassium hydroxide at 0°.[6] We have found the half-life for this reaction to be 16 hr at 0° under heterogeneous, aqueous reaction conditions. These experimental conditions are quite different from those employed

Scheme I



in carrying out the reactions with the other nucleophiles first discussed. Those reactions are carried out in alcohol solution at 50° (except the reaction using potassium amide in liquid ammonia) and are virtually complete in 2–3 hr. In contrast, the reaction of the carbinol **1** with hydroxide ion at 0° is slower, and if the reaction is carried out under homogeneous conditions in 80% ethanol–20% water at 0°, the half-life is nearly 600 hr (as measured by titration of aliquots of the base during the reaction).

We have determined the mechanisms by which phenyl(trichloromethyl)carbinol reacts with methoxide anion in methanol solution at 40°. This reaction was chosen for study because it is typical of the reactions of strong nucleophiles with (trichloromethyl)carbinols in alcoholic potassium hydroxide solutions at 50°. The 40° temperature and the shortened reaction time of 2 hr was chosen to minimize racemization reactions. The α-methoxyphenylacetic acid is formed in 75% yield when the reaction is carried out at 50° for 3–5 hr; the methoxy acid is easily isolated and purified; and the stereochemistry of the reaction can be studied and used to help elucidate the mechanism. The configurations are known of the optical isomers of the product, α-methoxyphenylacetic acid, and of the possible intermediate, α-chlorophenylacetic acid.

Pathway 1 (Scheme I) clearly involves one inversion of configuration at the α carbon whereas the second pathway should require two or three inversions depending on whether or not an α-lactone was involved in the replacement of chlorine by methoxide. The first inversion in pathway 2 would result from the opening of the epoxide ring by the attack of the migrating chlorine on the α carbon from the side opposite the departing epoxide oxygen. This step cannot be studied by itself in methanolic potassium hydroxide at 40°; however step **3**–**4** can be studied in methanolic potassium hydroxide at 40°, and 96% racemization occurs in a 2-hr period. This racemization is several times more rapid than the racemization of α-chlorophenylacetate anion itself under the same conditions and suggests the possibility of a ketene intermediate in going from **3** to **4** under basic reaction conditions.

Step **4**–**5** also can be studied by itself. This is a surprisingly slow reaction ($t_{1/2}$ = 7 hr) which follows first-order kinetics to at least 75% completion. This strongly indicates that the rate-controlling step must be α-lactone formation,[7] and in theory there must be two inversions in going from **4** to **5**. In reality, 96% of the material reacting by pathway 2 has been racemized by the time 4 has been formed, and **4** is racemized under the reaction conditions twice as fast as it reacts with methoxide (k_1 for racemization is 0.0038 min^{-1} and k_1 for **4** → **5** is 0.0017 min^{-1}, both at 40° in methanolic potassium hydroxide). Only 3% of the product **6**, isolated from the 2-hr reaction at 40°, is formed by pathway 2 (*vide infra*), and this combined with the successive partial racemizations listed above reduces to 1% the contribution pathway 2 makes to the final observed optical activity of **6**.

Pathway 2 is demonstrated to account for approximately 23% of the product by the detection of 20% of α-chlorophenylacetic acid in the crude α-methoxyphenylacetic acid when the reaction is carried out for 2 hr at 40°. A kinetic study of the displacement of chlorine by methoxide (**4** → **5**) at 40° shows the reaction to be sufficiently slow so that the formation of 23% of **4** would give rise to the observed 20% of **4** with 3% being converted to **5**. (However, at 50° for 15 hr, almost all of **4** is converted to **5**.)

Accordingly, under the above 40° reaction conditions, **1** must be converted into products (**4** + **6**) approximately 23% by pathway 2 with the balance going by pathway 1. As discussed above, most of that going by pathway 2 is trapped as **4**, and successive partial racemizations along this pathway cause the small amount of **6** formed to be almost completely racemized.

Experimentally, the final methoxy acid **6** is obtained with 9% inversion (91% racemization) and 99% of this optical activity must be assigned to pathway 1. The conversion of the carbinol **1** to **6** with inversion is consistent with pathway 1. The 91% racemization is attributed to the base-catalyzed racemization of intermediate methyl α-methoxyphenylacetate or α-methoxyphenylacetate anion. Control experiments with methyl (*R*)-(−)-α-methoxyphenylacetate confirm this.

Phenyl(trichloromethyl)carbinol was resolved by preparing phenyl(trichloromethyl)carbinyl hydrogen succinate and resolving this with quinine. The resolved quinine salt was converted back to the hydrogen succinate ester, and the optically active carbinol was obtained by acid-catalyzed hydrolysis of the succinate acid ester. The optically pure carbinol ($[\alpha]^{25}D$ +38°) was shown to have the *S* configuration by converting it in 9% yield to (*R*)-(+)-α-methylbenzyl alcohol (**7**) ($[\alpha]^{25}D$ +18.6°) of 37% optical purity by treatment with lithium and liquid ammonia.[8] The rotations[9] and configurations[10] of the α-methylbenzyl alcohols are well-known. Reduction of the levorotatory isomer of phenyl(trichloromethyl)carbinol, having an optical purity of 54%, gave (*S*)-**7** with an optical purity of 18% under the same reaction conditions. The crude **7** as isolated from the reduction consisted of 85% α-methylbenzyl alcohol, 11% β-phenethyl alcohol (*via* styrene oxide), and 4% acetophenone. The side reactions can cause no inversions of configuration and so the *S* configuration can be assigned with confidence to the dextrorotatory phenyl(trichloromethyl)carbinol. The large loss in optical purity during the reduction

is due to part of the carbinol being reduced to acetophenone. This occurs by an initial dehydrohalogenation of one of the chloro carbinols to a chloroacetophenone and the subsequent reduction of this to inactive α-methylbenzyl alcohol.

Experimental Section

Melting points and boiling points are corrected. The infrared spectra were recorded on a Beckman IR-8 infrared grating spectrophotometer and the nmr spectra on a Varian A-60A spectrometer. Chemical shift values are expressed as δ values (ppm) downfield from tetramethylsilane as internal standard. Rotations were measured on a Franz, Schmidt, and Haensch (Berlin S) polarimeter with a sodium lamp as a light source. Polarimeter tubes of 2-dm length were used; concentration terms are grams of solute per 100 ml of solution. Elemental microanalyses were performed by Dr. Franz J. Kasler and Mrs. Shelesa L. A. Brew.

Phenyl(trichloromethyl)carbinyl Hydrogen Succinate. Phenyl(trichloromethyl)carbinol[3] (226 g, 1.0 mol), 120 g (1.2 mol) of freshly distilled succinic anhydride, and 160 g (2.0 mol) of pyridine were heated on a steam bath for 24 hr and the hot solution was poured into 1 l. of benzene and allowed to cool. The benzene solution was washed with 3 *N* hydrochloric acid to remove the pyridine and then extracted with 5% sodium carbonate solution. The sodium carbonate extracts were concentrated on a "Roto-Vac" to remove the emulsified benzene and the clear solution was acidified with 6 *N* hydrochloric acid to yield 374 g of crude phenyl(trichloromethyl)carbinyl hydrogen succinate. After recrystallization from 2700 ml of cyclohexane, there was obtained 256 g of the pure material: mp 108–109°; ir (KBr) 3300–2600 (COOH), 1745 (C=O), 1708 (C=O), 1440, 1400, 1370, 1345, 1260, 1228, 1185, 1155, 1005, 930–900, 860, 790, 775, 740, 695, 670, 625, and 610 cm^{-1}; nmr (CH_2Cl_2) δ 11.2 (s, 1, COOH), 7.4 (m, 5, C_6H_5), 6.3 (s, 1, $CH(CCl_3)$), 2.7 (s, 4, $-CH_2CH_2-$).

Anal. Calcd for $C_{12}H_{11}O_4Cl_3$: C, 44.26; H, 3.41; Cl, 32.67. Found: C, 44.31; H, 3.50; Cl, 32.40.

Resolution of Phenyl(trichloromethyl)carbinyl Hydrogen Succinate. Phenyl(trichloromethyl)carbinyl hydrogen succinate (125 g, 0.38 mol), 125 g (0.30 mol) of quinine (N.F.), mp 162–166°, and 1300 ml of ethyl acetate were heated on a steam bath until nearly complete solution had taken place and then filtered to remove insoluble particles. After standing for 2 days at room temperature the crude phenyl(trichloromethyl)carbinyl hydrogen succinate quinine salt [122 g, mp 149–152°, $[\alpha]^{25}D$ −82° (c 1.06, EtOH)] was filtered and the last traces of ethyl acetate were pressed out with a rubber dam. The quinine salt was dissolved in 3.5 l. of ethyl acetate; after standing for 1 day at room temperature, 71 g of the crystalline quinine salt was obtained: mp 155–156°; $[\alpha]^{26}D$ −66° (c 1.01, EtOH). The 3.5 l. of the ethyl acetate mother liquor was placed in a cold room overnight and an additional 18 g of crude quinine salt ($[\alpha]^{26}D$ −72°) was obtained. Three further recrystallizations of a 5-g sample of the quinine salt with an $[\alpha]^{25}D$ of −66° from ethyl acetate gave products with rotations of −63.7, −64.0, and −63.7°, respectively.

The ethyl acetate mother liquor from the precipitation of the levorotatory quinine salt of phenyl(trichloromethyl)carbinyl hydrogen succinate was reduced in volume from 1300 to 400 ml, cooled to 0° overnight, filtered to remove a slight precipitate, and then evaporated to dryness on a steam bath. The residue, which contained the other diastereoisomer, was a dark brown, tacky material which could not be induced to crystallize but was satisfactory for the preparation of *l*-phenyl(trichloromethyl)carbinyl hydrogen succinate having an optical purity of 53%.

The phenyl(trichloromethyl)carbinyl hydrogen succinate quinine salt ($[\alpha]^{26}D$ −66°) was converted to (*S*)-(+)-phenyl(trichloromethyl)carbinyl hydrogen succinate by dissolving 79 g (0.12 mol) in 300 ml of hot ethanol and slowly adding this solution with stirring to 300 ml of 1 *N* hydrochloric acid and an equal amount of ice. A white solid formed which made stirring difficult. The solid was removed by decantation and dissolved in benzene. The aqueous solution was extracted twice with 500-ml portions of benzene and the combined benzene solutions were washed with water, dried ($MgSO_4$), and concentrated to a clear, glassy material (36 g, 90%). A small portion was recrystallized from cyclohexane to give **(*S*)-(+)-phenyl(trichloromethyl)carbinyl hydrogen succinate:** mp 66–68°; $[\alpha]^{25}D$ +62° (c 2.1, EtOH). The ir and nmr spectra were the same as for the racemic compound.

(*S*)-(+)-Phenyl(trichloromethyl)carbinol. To 36 g (0.11 mol) of (*S*)-(+)-phenyl(trichloromethyl)carbinyl hydrogen succinate dissolved in 120 ml of glacial acetic acid was added 100 ml of water and 16 ml of concentrated hydrochloric acid. The mixture was refluxed in an oil bath for 6 hr and cooled, an equal amount of water was added, and the resultant solution was extracted with two 500-ml portions of carbon tetrachloride. The combined carbon tetrachloride extracts were washed twice with sodium bicarbonate solution and twice with water, dried ($MgSO_4$), and concentrated to yield 17.1 g (69% yield from the acid ester, 15% from the racemic carbinol) of (*S*)-(+)-phenyl(trichloromethyl)carbinol: bp 149–151° (14 mm); $[\alpha]^{25}D$ +38° (c 5.0, EtOH). The ir and nmr spectra were the same as for the racemic compound.

In the same manner the impure quinine salt of the (*R*)-(−)-phenyl(trichloromethyl)carbinyl hydrogen succinate was converted to 20 g of (*R*)-(−)-phenyl(trichloromethyl)carbinol: $[\alpha]^{25}D$ −20.6° (c 10.1, EtOH); this rotation corresponds to an optical purity of 53%.

Reduction of (*S*)-(+)-Phenyl(trichloromethyl)carbinol to (*R*)-(+)-α-Methylbenzyl Alcohol. To a stirred solution of 5 g (0.022 mol) of (*S*)-(+)-phenyl(trichloromethyl)carbinol ($[\alpha]^{25}D$ +38°) in 1500 ml of liquid ammonia was added 1 g (0.14 g-atom) of lithium metal that had been cut into small pieces. After about 1.5 min the blue color appeared, and 24 g (0.3 mol) of ammonium nitrate dissolved in 200 ml of liquid ammonia was added to destroy any unreacted lithium metal and also to destroy the lithium amide formed during the reaction. The liquid ammonia was allowed to evaporate and to the dark residue was added 200 ml of 2 *N* hydrochloric acid. The acid solution was extracted with two 100-ml portions of ether; the combined extracts were washed with three portions of water, dried ($MgSO_4$), and distilled to give 0.25 g (9% yield) of (*R*)-(+)-α-methylbenzyl alcohol: bp 84–85° (8 mm); $[\alpha]^{25}D$ +18.6° (c 5.0, toluene). The literature value[11] for (*S*)-(−)-α-methylbenzyl alcohol is $[\alpha]^{27}D$ −50.6° (c 3, toluene). The nmr spectrum showed the product to consist of 85% α-methylbenzyl alcohol, 11% β-phenethyl alcohol (*via* styrene oxide), and 4% acetophenone.

Conversion of (*S*)-(+)-Phenyl(trichloromethyl)carbinol to (*R*)-(−)-α-Methoxyphenylacetic Acid. Over a 90-min period, 4.9 g (0.088 mol) of potassium hydroxide dissolved in 100 ml of methanol was added to a stirred solution of 5 g (0.022 mol) of (*S*)-(+)-phenyl(trichloromethyl)carbinol ($[\alpha]^{25}D$ +38°) in 35 ml of methanol. The temperature was maintained at 40–42°. After the addition was complete, the reaction mixture was stirred for an additional 30 min. The solution was then cooled, the precipitated potassium chloride filtered off, and the alkaline methanol solution diluted with an equal volume of water and extracted with three 100-ml portions of ether. The combined ether extracts were dried ($MgSO_4$), concentrated, and distilled to yield 2.63 g (53% recovery) of (*S*)-(+)-phenyl(trichloromethyl)carbinol having the same rotation as the starting material. The aqueous alkaline solution was acidified to pH 1 with dilute hydrochloric acid, extracted with three 100-ml portions of ether, and dried ($MgSO_4$); the ether was evaporated to give a residue of 0.6 g. This was dissolved in 20 ml of chloroform and extracted with three 10-ml portions of water to remove mandelic acid. The chloroform solution was dried ($MgSO_4$) and evaporated to give 0.51 g (13.5% yield, or 29% allowing for recovered carbinol) of α-methoxyphenylacetic acid. This was recrystallized (decolorizing carbon) from 15 ml of cyclohexane. There was obtained 0.21 g of (*R*)-(−)-α-methoxyphenylacetic acid: mp 67–68° [lit. 65–66° for *R*-(−),[12] 71–72° for *RS*[13]]; $[\alpha]^{25}D$ −13.1° (c 4.1, EtOH) [lit.[12] $[\alpha]^{20}D$ −150.7° (c 0.57, EtOH)]. The $[\alpha]^{25}D$ of −13.1° is equal to an optical purity of 8.7%. The nmr and ir spectra were identical with spectra of authentic α-methoxyphenylacetic acid.

In the same manner, 5 g of (*R*)-(−)-phenyl(trichloromethyl)carbinol ($[\alpha]^{25}D$ −20.6°) was converted to 0.22 g of (*S*)-(+)-α-methoxyphenylacetic acid, mp 64–65°, with an $[\alpha]^{25}D$ of +18° (c 4.0, 20% ethanol).

In another experiment 5 g of racemic phenyl(trichloromethyl)carbinol was allowed to react with methanolic potassium hydroxide as above, but the crude acid fraction (1.3 g) was studied by nmr to determine the amount of α-chlorophenylacetic acid present. The α-CH signals (CCl_4) for the α-chloro acid, mandelic acid, and the α-methoxy acid occur at δ 5.27, 5.13, and 4.65, respectively, and the observed area ratios are 20:12:68.

In another experiment, 5 g of racemic phenyl(trichloromethyl)carbinol was allowed to react with stronger methanolic potassium hydroxide (containing 6.6 g of base, 0.1 mol) as above except at 50°. The reaction mixture was stirred at this temperature for 3 hr after the addition of base was completed and was then allowed to stand overnight at 50°. Under these conditions all of intermediate

chloro acid was converted to the methoxy acid. The crude acid was obtained as an oil which set up to a crystalline solid, mp 53–58° (3.35 g, theory 3.65 g), and its nmr spectrum was that of the pure α-methoxy acid. The α-CH nmr signal was at δ 4.65, and the α-CH signals of the mandelic acid (δ 5.13) and of the α-chloro acid (δ 5.27) were too small to be measured.

Racemization of Methyl (*R*)-(−)-α-Methoxyphenylacetate. A methanolic solution of potassium hydroxide was prepared by dissolving 6.7 g (0.12 mol) of potassium hydroxide in 200 ml of methanol. To this stirred solution at 40° was added, dropwise over a period of 1.3 hr, 1 g (0.0055 mol) of methyl (*R*)-(−)-α-methoxyphenylacetate in 70 ml of methanol. The ester had an $[\alpha]^{25}D$ of −88.5° (*c* 2.5, acetone) and was prepared by methylating (*R*)-(−)-mandelic acid with methyl iodide and silver oxide.[14] The literature value for this ester is $[\alpha]^{24}D$ −89.1° (*c* 1.11, acetone).[15] The mixture was stirred an additional 30 min at 40° and was then cooled and diluted with an equal volume of water. The solution was saturated with potassium chloride and extracted with two 100-ml portions on ether to remove any unreacted ester. The aqueous solution was acidified with dilute hydrochloric acid to pH 1 and extracted with three 100-ml portions of ether; the combined ether extracts were dried ($MgSO_4$) and evaporated to give 0.81 g of residue (89% yield). This α-methoxyphenylacetic acid was dissolved in cyclohexane, treated with decolorizing carbon, and chilled overnight near 0°. There was obtained 0.34 g of α-methoxyphenylacetic acid: mp 65–66°; $[\alpha]^{25}D$ −25.6° (*c* 4.0, EtOH). This represented a 17% retention of optical activity.[12] The nmr and ir spectra were identical with spectra of the authentic α-methoxyphenylacetic acid.

(*R*)-(−)-α-Chlorophenylacetyl Chloride. The following new preparation of the chloro acid chloride is a modification of Coll's procedure[16] for preparing the chloro acid from mandelic acid. Thionyl chloride (44 g, 0.374 mol) was dissolved in 200 ml of carbon tetrachloride, the solution was cooled to 5°, and 27 g (0.374 mol) of dimethylformamide was added over a 10-min period so the temperature did not exceed 7°. After stirring for 30 min in an ice bath, 20 g (0.135 mol) of (*S*)-(+)-mandelic acid [$[\alpha]^{27}D$ +152.9° (*c* 19.7, EtOH); mp 126–133°] was added at such a rate that the temperature did not exceed 7°; the reaction mixture was stirred at 4–7° for 1 hr and then allowed to warm up to room temperature during the next 2 hr. The resultant solution was poured over 200 ml of ice and quickly shaken. The carbon tetrachloride layer was separated, washed a second time with 200 ml of ice water, dried ($MgSO_4$), concentrated, and distilled to give 17 g (77% of theory) of (*R*)-(−)-chlorophenylacetyl chloride: bp 85–88° (2 mm); $[\alpha]^{31}D$ −160° (*c* 20.4, CCl_4) [lit.[17] bp 120° (23 mm); lit.[17] $[\alpha]^{17}D$ +158° (*c* 6, CS_2) for dextrorotatory isomer].

The $[\alpha]^{31}D$ rotation of −160° corresponds to an optical purity of 65% as determined by adding a 5-g sample to 50 ml of cold water and allowing the solution to stand overnight at room temperature. The (*R*)-(−)-α-chlorophenylacetic acid obtained had an $[\alpha]^{30}D$ of −122.3° (*c* 14.3, EtOH) and a melting point of 58–60° [lit.[18] mp 60–61°; lit.[18] $[\alpha]^{12}D$ −191° (*c* 3.35, benzene)]. The chloro acid chloride gave the following spectral data: ir (neat) 3070, 3040, 2980, 1810, (C=O), 1780, 1500, 1460, 1180, 1045, 1005, 980, 840, 790, 760, and 700 cm^{-1}; nmr (CCl_4) δ 7.35 (s, 5, Ph), 5.56 (s, 1, α-CH).

Reaction of (*R*)-(−)-α-Chlorophenylacetyl Chloride with Methanolic Potassium Hydroxide. A 5-g (0.026-mol) sample of the chloro acid chloride ($[\alpha]^{31}D$ −159°, 65% optical purity) was added dropwise over a period of 90 min to methanolic potassium hydroxide prepared by dissolving 6 g (0.106 mol) of potassium hydroxide in 100 ml of methanol. The temperature was maintained at 40°. After the addition was completed, the reaction mixture was stirred for an additional 30 min. The solution was then cooled with ice, diluted with an equal volume of water, acidified to pH 1 with dilute hydrochloric acid, and extracted with three 100-ml portions of ether. The ether was dried ($MgSO_4$) and evaporated to give a residual oil (4.3 g) which solidified on standing to give crystals, mp 65–75°. This was shown to be 95% α-chlorophenylacetic acid and 5% α-methoxyphenylacetic acid by comparing the nmr signals ($DCCl_3$) at δ 5.35 (–CHCl–) and 4.71 (–C*H*OCH_3–). The $[\alpha]^{33}D$ of the mixture was −4.1° (*c* 14.4, EtOH) [lit.[18] −191° (*c* 3.35, benzene)] corresponding to over 96% racemization.

Anal. Calcd for $C_8H_7O_2Cl$: C, 56.3; H, 4.1; Cl, 20.8. Calcd for $C_8H_7O_2(OCH_3)$: C, 65.0; H, 6.03. Found: C, 56.39; H, 4.38; Cl, 19.98.

Racemization of (*S*)-(+)-α-Chlorophenylacetic Acid. The acid [1.1 g, $[\alpha]^{31}D$ +37.5° (20% optically pure)][19] was dissolved in 25 ml of methanol containing 1 g of potassium hydroxide and thermostated at 40° for 3 hr. The acid mixture was isolated as before by acidification and extraction with ether. The oily acid was dissolved in chloroform and washed with water to remove mandelic acid. There was obtained 1 g of recovered acid analyzing (nmr) for 84% α-chloro acid and 16% α-methoxy acid, $[\alpha]^{32}D$ +18.5°. This corresponds to 50% racemization at 40° in 3 hr, equal to a first-order *k* of 3.8×10^{-3} min^{-1}.

Kinetic Measurements with α-Chlorophenylacetic Acid. Ten 2-ml aliquots from a solution of 2.14 g of α-chlorophenylacetic acid and 1.85 g of potassium hydroxide in 50 ml of methanol, thermostated at 40°, were titrated with 0.1 *N* hydrochloric acid over a 13-hr period. The log of the fraction of unreacted chloro acid was plotted against time. A linear plot was obtained with $t_{1/2}$ equal to 7 hr and a first-order *k* of 1.7×10^{-3} min^{-1}. From this the calculated values for the extent of the reaction at various times are 12% in 75 min and 19% in 2 hr. Seventy-five minutes is the average time of reaction for α-chlorophenylacetic acid formed from the carbinol in the 2-hr reaction described above consisting of 90-min addition time followed by 30-min additional reaction time.

Methyl phenyl(trichloromethyl)carbinyl ether was prepared by allowing 30 g (0.13 mol) of racemic phenyl(trichloromethyl)carbinol to react with 60 g (0.42 mol) of methyl iodide in 100 ml of anhydrous ether and 36 g (0.16 mol) of silver oxide for 12 hr with stirring at room temperature. There was obtained 19 g (80% yield) of methyl phenyl(trichloromethyl)carbinyl ether: mp 54–55° [lit.[20] mp 58°]; nmr (CCl_4) δ 7.48 (m, 5, C_6H_5), 4.60 (s, 1, >CH–), and 3.38 (s, 3, $-OCH_3$).

Registry No.—(*S*)-(+)-**1**, 53432-38-5; (*S*)-(+)-1 hydrogen succinate, 53432-41-0; (*S*)-(+)-1 hydrogen succinate quinine salt, 53432-42-1; (*R*)-(−)-**1**, 53432-39-6; (*R*)-(−)-1 hydrogen succinate, 53432-43-2; (*R*)-(−)-1 hydrogen succinate quinine salt, 53432-44-3; (±)-**1**, 53495-27-5; (*R*)-(−)-**3**, 53432-40-9; (*R*)-(−)-**6**, 3966-32-3; (*S*)-(+)-**6**, 26164-26-1; (*R*)-(−)-**6** Me ester, 32174-46-2; (*R*)-(+)-**7**, 1517-69-7; succinic anhydride, 108-30-5; quinine, 130-95-0; (*R*)-(−)-mandelic acid, 611-71-2; (*S*)-(+)-mandelic acid, 17199-29-0; (*R*)-(−)-α-chlorophenylacetic acid, 43195-94-4; (*S*)-(+)-α-chlorophenylacetic acid, 29125-24-4; racemic α-chlorophenylacetic acid, 39266-56-3.

References and Notes

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(8) Before choosing the lithium–liquid ammonia procedure for reducing the trichloromethyl group to methyl, the usefulness of potassium, sodium, zinc, Raney nickel, and catalytic methods was studied in an effort to accomplish this conversion more efficiently. Catalytic hydrogenation over platinum oxide, 5% palladium on carbon, or 20% palladium on carbon failed. Reduction proceeded to the dichlorocarbinol stage and then stopped. A fourfold excess of Raney nickel was refluxed with a methanolic solution of phenyl(trichloromethyl)carbinol but only (dichloromethyl)phenylcarbinol could be detected. Zinc and acetic acid, or a zinc–copper couple in ethanol, gave (dichloromethyl)phenylcarbinol, β,β-dichlorostyrene, and β-chlorostyrene. Potassium and liquid ammonia gave primarily acetophenone. With sodium and liquid ammonia a mixture of α-methylbenzyl alcohol and acetophenone was formed. After dissolving sodium in liquid ammonia to give the characteristic blue solution and then adding phenyl(trichloromethyl)carbinol, only acetophenone was formed. The above results indicate that the reduction is occurring with the carbinol adsorbed on the surface of the alkali metal, and the slower disolving lithium metal gives better results because the adsorbed (trichloromethyl)carbinol is present on the metallic surface for a longer time. The reduction of the methyl ether of **1** using the above reagents was also studied, but without success.
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A General Route to Methoxy-Substituted Arylphosphonous Dichlorides *via* Mild Lewis Acid Catalysts

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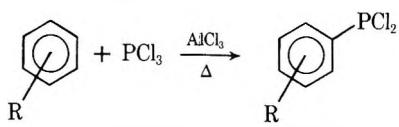
Treatment of anisoles 3 with phosphorus trichloride in the presence of catalytic amounts of anhydrous stannic chloride provides a convenient route to a variety of methoxy-substituted arylphosphonous dichlorides. Stannic chloride has been proven superior as a Friedel–Crafts catalyst for this reaction as compared to the previously reported use of aluminum chloride, ferric chloride, or zinc chloride. Substituent directive effects of polysubstituted anisoles have also been investigated.

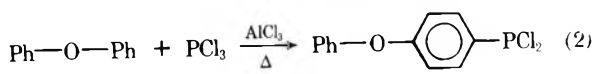
The introduction of the phosphonous dichloride moiety (PCl_2) into aromatic rings has been a topic of study for nearly 100 years.[1] Despite improvements in isolation and purification procedures, the Friedel–Crafts reaction of phosphorus trichloride with aromatic rings in the presence of an aluminum chloride catalyst remains a difficult, time-consuming, poor yield process[2] (eq 1). In cases where the aromatic ring is substituted by an ortho–para–directing group (alkyl, halogen, etc.), the reaction proceeds to yield the corresponding arylphosphonous dichloride, although the ortho–para–product ratios for substitution have been suspect due to lack of vigorous spectral methods of identification.[3]

In contrast, where the aromatic ring is substituted by a meta-directing group (NO_2, C(=O)R, etc.), the reaction fails completely; where the ring is substituted by a strongly activating group (NR_2), no catalyst is required.[4]



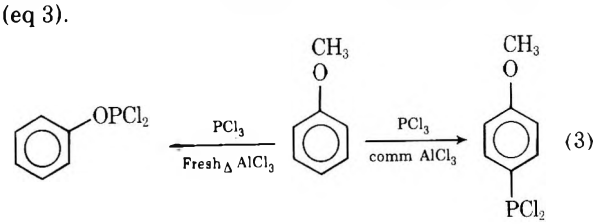
(1)

In cases where the aromatic ring is activated by OR, the overall reaction scheme is less well-defined. The reaction of diaryl ethers with phosphorus trichloride in the presence of aluminum chloride gives the para-substituted phosphonous dichlorides[5] (no ortho substitution found) (eq 2).



(2)

Where the reactant has been an *alkyl aryl* ether, however, the literature gives conflicting results. Michaelis[6] and Kunz[7] both reported that anisole, upon treatment with phosphorus trichloride and so-called "commercial" aluminum chloride, affords *p*-anisylphosphonous dichloride. Repetition of the reaction with freshly prepared aluminum chloride is reported to give the phenylphosphorodichloridite (eq 3).

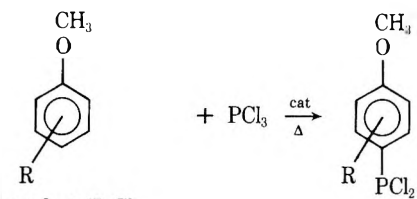


(3)

Other investigators have since found that this apparently straightforward reaction is useful for the preparation of *p*-anisylphosphonous dichloride.[8] In our hands, however, only the phosphorodichloridite (resulting from cleavage of the methyl ether followed by attack of phosphorus trichloride) could be isolated, despite repeated attempts with aluminum chloride.[9]

Clearly, a milder, more selective procedure for the introduction of the PCl_2 group into alkyl aryl ethers was desirable. The use of "deactivated" aluminum chloride (partially hydrated) was reviewed by Kosolapoff,[10] but no precise description of its preparation was given. Attempts to prepare $AlCl_3 \cdot X H_2O$ (by allowing anhydrous aluminum chloride to stand in air for several minutes up to several hours) gave a catalyst which was ineffective in the reaction under study (eq 3).

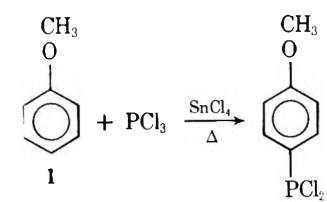
Since aluminum chloride is known to cleave alkyl aryl ethers,[11] a weaker Lewis acid catalyst was considered. Two reports of the use of zinc chloride[12] and ferric chloride[13] as catalysts for the reaction of anisoles with phosphorus trichloride have previously appeared, despite claims to the contrary.[14] However, neither author investigated the scope of the reaction. Poor yields, large amounts of undistillable residues, and formation of triaryl phosphines limited the use of these catalysts in preparation of arylphosphonous dichlorides to only two substrates, anisole[13] and 1,3-dimethoxybenzene[12,13] (eq 4).



(4)

R = H; catalyst $FeCl_3$
R = OCH_3; catalyst $ZnCl_2$

Both zinc chloride and ferric chloride give nonhomogeneous reaction mixtures, a fact which may contribute to isolation and purification problems. To avoid these difficulties, an alternative Friedel–Crafts catalyst was utilized. Stannic chloride[15] (anhydrous, organic soluble) in the presence of phosphorus trichloride and anisole 1 gave a 91%



1 2 (91%)

yield of phosphonous dichloride, no ether cleavage (and subsequent formation of phenylphosphorodichloridite), and a minimum of undistillable residue.[16,17]

Table I
Phosphonous Dichlorides 4 from Anisoles 3

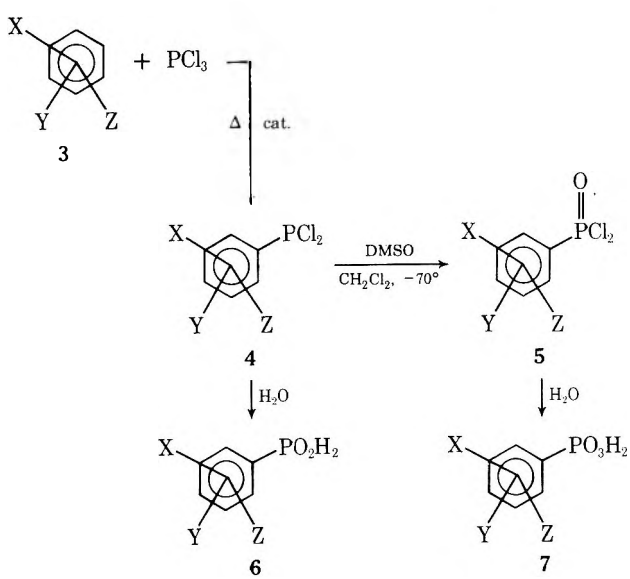
Compd	Anisole X	Anisole Y	Anisole Z	Catalyst (rxn time)	Yield,[a] %	Phosphonous dichloride[b]	Bp, °C (mm)	Nmr (CCl_4 or $CDCl_3$)
3a	OCH_3	H	H	$SnCl_4$ (76 hr)	91	4-$CH_3OC_6H_4$- (4a)	74–78 (0.05)[c]	3.78 (s, 3), 6.90 (dd, 2, J = 9 and 2 Hz), and 7.75 ppm (t, 2, J = 9 Hz)
				$FeCl_3$ (44 hr)	31			
3b	SCH_3	H	H	$SnCl_4$ (80 hr)	36	4-$CH_3SC_6H_4$- (4b)	98–103 (0.02)	2.5 (s, 3), 7.15 (dd, 2, J = 9 and 2 Hz), and 7.7 ppm (t, 2, J = 9 Hz)
				$FeCl_3$ (60 hr)	19			
3c	OCH_3	2-CH_3	H	$SnCl_4$ (16 hr)	68	4-CH_3O-3-CH_3-C_6H_3- (4c)	103–106 (0.07)	2.3 (s, 3), 3.9 (s, 3), 6.8 (dd, 1, J = 9 and 2 Hz), and 7.5–7.9 ppm (m, 2)
3d	OCH_3	2-OCH_3	H	$SnCl_4$ (15 hr)	26	3-CH_3O-4-CH_3O-C_6H_3- (4d)	112–115 (0.4)	3.75 (s, 3), 3.80 (s, 3), 6.8 (dd, 1, J = 9 and 2 Hz), and 7.0–7.5 ppm (m, 2)
				$FeCl_3$ (24 hr)				
3e	OCH_3	3-OCH_3	H	$FeCl_3$ (14 hr)	29	2-CH_3O-4-OCH_3-C_6H_3- (4e)	114–118 (0.05) mp 46–7[d]	3.80 (s, 3), 3.85 (s, 3), 6.3 (dd, 1, J = 4 and 2 Hz), 6.5 (dd, 1, J = 9.2 Hz), and 7.8 ppm (dd, 1, J = 10, 4 Hz)
3f	OCH_3	3-CH_3	H	$SnCl_4$ (49 hr)	71	4-CH_3O-2-CH_3-C_6H_3- and 4-CH_3-2-CH_3O-C_6H_3- (1:1) (4f)	93–97 (0.1)	2.4 (s, 3, 4-CH_3 isomer), 2.6 (d, 3, J = 3 Hz, 2-CH_3 isomer), 3.8 (s, 3, 2-CH_3 isomer), 3.9 (s, 3, 4-CH_3, isomer), 6.6–7.05 (m, 4), and 7.7–8.2 ppm (m, 2)
3g	OCH_3	2-OCH_3	4-OCH_3	$FeCl_3$ (40 hr)	26	2,4,5-CH_3O-C_6H_2- (4g)	136–140 (0.04)	3.9 (s, 9), 6.5 (d, 1, J = 6 Hz), and 7.48 (d, 1, J = 3 Hz)
3h	OCH_3	2-CH_3	3-CH_3	$SnCl_4$ (96 hr)	72	4-CH_3O-2,3-CH_3-C_6H_2- (4h)	108–111 (0.09)	2.1 (s, 3), 2.5 (s, 3), 3.8 (s, 3), 6.75 (d, 1, J = 9 Hz), and 7.88 ppm (dd, 1, J = 9 and 3 Hz)
3i	OCH_3	2-CH_3	4-CH_3	$SnCl_4$ (40 hr)	50	2-CH_3O-3,5-CH_3-C_6H_2- (4i)	110–120 (0.05)	2.35 (s, 6), 3.9 (s, 3), 6.7 (d, 1, J = 6 Hz), and 7.6 ppm (d, 1, J = 4 Hz)
				$FeCl_3$ (60 hr)				
3j	OCH_3	2-CH_3	3-OCH_3	$SnCl_4$ (72 hr)	31	2,4-CH_3O-3-CH_3-C_6H_2- (4j)	128–137 (0.4)	2.15 (s, 3), 3.8 (s, 6), 6.75 (d, 1, J = 8 Hz), and 7.75 ppm (dd, 1, J = 8 and 3 Hz)
3k	OCH_3	3-C_2H_5	H	$SnCl_4$ (85 hr)	71	4-CH_3O-2-C_2H_5-C_6H_3- and 2-CH_3O-4-C_2H_5-C_6H_3 (1:1) (4k)	94–100 (0.1)	1.0–1.4 (m, 6), 2.3–3.2 (m, 4), 3.7 (s, 3), 3.8 (s, 3), 6.5–7.0 (m, 4), 7.6–8.1 (m, 2)

Table I
(Continued)

Compd	Anisole X	Anisole Y	Anisole Z	Catalyst (rxn time)	Yield,[a] %	Phosphonous dichloride[b]	Bp, °C (mm)	Nmr (CCl_4 or $CDCl_3$)
3l	OCH_3	3-$(CH_3)_2CH$	H	$SnCl_4$ (148 hr)	55	4-CH_3O-2-$(CH_3)_2CH$-C_6H_3- and 2-CH_3O-4-$(CH_3)_2CH$-C_6H_3- (1:3) (41)[e]	95–96 (0.05)	1.0–1.4 (m, 12), 2.6–3.2 (m, 2), 3.8 (s, 3), 3.9 (s, 3), 6.7–7.1 (m, 4), and 7.7–8.2 (m, 2)
3m	OCH_3	3-$(CH_3)_3C$-	H	$SnCl_4$ (88 hr)	26	2-CH_3O-4-$(CH_3)_3C$-C_6H_3- (4m)	103–110 (0.10)	1.3 (s, 9), 3.9 (s, 3), 6.8, 7.3 (m, 2), and 7.8 ppm (dd, 1, J = 8 and 4 Hz)
3n	O-n-C_4H_9	H	H	$SnCl_4$ (114 hr)	72	4-n-C_4H_9O-C_6H_4- (4n)	107–110 (0.10)	0.8–2.0 (m, 7), 4.0 (t, 2, J = 7 Hz), 7.0 (dd, 2, J = 9.2 Hz), and 7.9 ppm (t, 2, J = 9 Hz)
3o	OC_2H_5	H	H	$FeCl_3$ (133 hr)	55	4-C_2H_5O-C_6H_4- (4o)	78–87 (0.10)[f]	1.4 (t, 3, J = 7 Hz), 4.05 (q, 4, J = 7 Hz), 7.0 (dd, 2, J = 9.1 Hz), and 7.8 ppm (t, 2, J = 9 Hz)
3p	O-n-C_3H_7	H	H	$SnCl_4$ (90 hr)	72	4-n-C_3H_7O-C_6H_4- (4p)	92.8 (0.10)	1.0 (t, 3, J = 7 Hz), 1.8 (sextet, 2, J = 7 Hz), 3.9 (t, 2, J = 7 Hz), 7.0 (dd, 2, J = 9.2 Hz), and 7.8 ppm (t, 2, J = 9 Hz)

[a] Figure refers to distilled, pure material. [b] Satisfactory elemental analyses (±9.3%) were obtained for all new compounds. [c] Lit.[8] bp 140–141° (11 mm). [d] Lit.[13] bp 175–180° (12–15 mm). [e] Careful distillation effected separation of the isomer present in larger amount; nmr of 2-CH_3O-4-$(CH_3)_2CH$-C_6H_3-: 1.35 (d, 6, J = 7 Hz), 2.95 (sextet, 1, J = 7 Hz), 3.9 (s, 3). [f] Lit.[22] bp 266°.

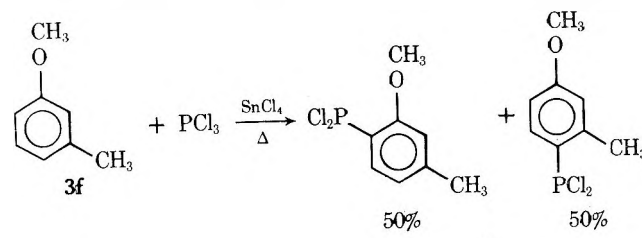
This reaction has been extended to include a variety of substituted anisoles Table I). In several cases, ferric chloride was also used as the catalyst for comparative purposes. Structures of the phosphonous dichlorides were readily determined from the nmr spectra,[18] combustion analyses, and conversion[19] to the corresponding phosphonic dichlorides



5, phosphinic acids **6**, and hydrolysis of the phosphonic dichlorides to the free phosphonic acids **7** (Table II).

An examination of the directive effects of the methoxyl groups suggests a logical pattern for electrophilic attack by phosphorus trichloride on the ring. The parent anisole **3a** gives only substitution para to methoxyl. No ortho substitution has been observed.[20] A similar result is obtained with *o*-methylanisole (**3c**). Introduction of the phosphonous dichloride moiety occurs only para to the methoxyl group. No substitution is seen at the positions ortho to methoxyl or para to methyl.[21]

In contrast, *m*-methylanisole (**3f**) undergoes reaction at both the positions ortho and para to methoxyl (para and



ortho to methyl, respectively) in approximately equal amounts.

This suggests that the meta-methyl group may be hindering attack ortho to methyl by the rather bulky electro-

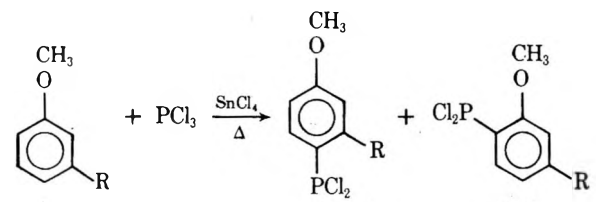
Table II
Phosphinic Acids 6 and Phosphonic Acids 7 from Phosphonous Dichlorides 4

Phosphonous dichloride 4	Phosphonic acid[a] 6	mp, °C 7	Nmr (DMSO-d_6) of phosphonic acid
4a	112–114[b]	168–169[c]	3.70 (s, 3), 6.95 (dd, 2, J = 9 and 3 Hz), 7.68 (dd, 2, J = 13 and 9 Hz), and 10.8 ppm (s, 2, position variable)
	6a	7a	
4b	105–106	168–169	2.6 (s, 3), 7.3–8.0 (m, 4), and 11.0 ppm (position variable)
	6b	7b	
4c	68–70	183–184	2.2 (s, 3), 3.8 (s, 3), 7.0 (dd, 1, J = 9 and 3 Hz), 7.55 (ddd, 1, J = 12, 9, and 1.5 Hz), 7.50 (dd, 1, J = 12 and 2 Hz), and 10 ppm (s, 2, position variable)
	6c	7c	
4d	138–139		3.75 (s, 6), 6.9–7.5 (m, 3), 10.3 (s, 1, position variable), and 7.5 ppm (d, 1, J = 540 Hz)[d]
	6d	7d	
4e	147–148[e]	163–163.5[f]	2.7 (s, 6), 6.4–6.7 (m, 2), 7.55 (dd, 1, J = 16 and 9 Hz), and 10.5 ppm (s, 2, position variable)
	6e	7e	
4f	108–108.5[g]	185–186[h]	2.55 (s, 3), 3.90 (s, 3), 6.75–7.0 (m, 2), 7.8 (dd, 1, J = 16 and 9 Hz) and 9.6 ppm (s, 2); 2.3 (s, 3), 3.75 (s, 3), 6.6–7.0 (m, 2), 7.5 (dd, 1, J = 15 and 8 Hz), and 10.6 ppm (s, 2)[k]
	154–155[i]	160–161[j]	
	6f	7f	
4g			
4h	141–142	167–168	2.10 (s, 3), 2.47 (s, 3), 3.80 (s, 3), 6.80 (dd, 1, J = 9 and 3 Hz), 7.65 (dd, 1, J = 13 and 9 Hz), and 8.8 (s, 2, position variable)
	6h	7h	
4i	150–151		
	6i		
4j	140–141	168	2.0 (s, 3), 3.65 (s, 3), 3.75 (s, 3), 6.70 (dd, 1, J = 8 and 3 Hz), 7.5 (dd, 1, J = 14 and 8 Hz), and 8.4 ppm (s, 2, position variable)
	6j	7j	
4k			
4l			
4m	164–166		1.4 (s, 9), 3.9 (s, 3), 7.0–7.2 (m, 2), 7.4–7.8 (m, 1), 8.0 (s, 1, position variable), and 7.7 ppm (d, 1, J = 545 Hz)[d]
	6m		
4n			
4o	118[l]		

[a] Satisfactory elemental analyses (±0.3%) were obtained for all new compounds. [b] Lit.[23] mp 113–114°. [c] Lit.[23] mp 158°. *Anal.* Calcd for $C_7H_7O_4P$: C, 44.75; H, 4.78. Found: C, 44.67; H, 4.85. [d] Spectrum of phosphinic acid. [e] Lit.[12] mp 160–161°. *Anal.* Calcd for $C_8H_{11}O_4P$: C, 47.51; H, 5.44. Found: C, 47.74; H, 5.25. [f] Lit.[12] mp 165–166°. *Anal.* Calcd for $C_8H_{11}O_5$: C, 44.06; H, 5.05. Found: C, 44.31; H, 5.13. [g] Isomers could be fractionally crystallized apart; mp for 2-CH_3-4-CH_3O-$C_6H_3PO_2H_2$. *Anal.* Calcd for $C_8H_{11}O_3P$: C, 51.70; H, 5.92. Found: C, 51.65; H, 5.97. [h] Isomers could be fractionally crystallized apart; mp for 2-CH_3-4-CH_3O-$C_6H_3PO_3H_2$. *Anal.* Calcd for $C_8H_{11}O_4P$: C, 47.5; H, 5.44. Found: C, 47 44; H, 5.50. [i] Isomers could be fractionally crystallized apart; mp for 2-CH_3O-4-CH_3-$C_6H_3PO_2H_2$. *Anal.* Calcd for $C_8H_{11}O_3P$: C, 51.70; H, 5.92. Found: C, 51.65; H, 5.92. [j] Isomers could be fractionally crystallized apart; mp for 2-CH_3O-4-CH_3-$C_6H_3PO_3H_2$. *Anal.* Calcd for $C_8H_{11}O_4P$: C, 47.51; H, 5.44. Found: C, 47.46; H, 5.57. [k] Nmr spectra for 2-CH_3-4-CH_3O-$C_6H_3PO_3H_2$ and 2-CH_3O-4-CH_3-$C_6H_3PO_3H_2$, respectively. [l] Lit.[23] mp 115°.

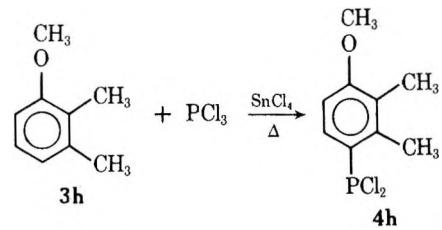
phile (presumably $PCl_2^+SnCl_5^-$) sufficiently to force some reaction to the position ortho to methoxyl (para to methyl).

To study the influence of steric hindrance in this reaction, three other meta-substituted anisoles were subjected to the reaction conditions with results consistent with the increased hindrance at the meta position. Successively increased hindrance at the meta position eventually gives substitution *only ortho* to methoxyl as in **4m.**



3k, R = Et — **4k**, 50% — 50%
l, R = *i*-Pr — **l**, 24% — 76%
m, R = *t*-Bu — **m**, 0% — 100%

An exception to this trend appeared, however, when 2,3-dimethylanisole was subjected to the reaction conditions. Based on analogy with **3f, 3k, 3l,** and **3m,** it was expected that approximately equal quantities of the two isomeric phosphonous dichlorides would be formed. Instead, only one isomer was formed, *i.e.*, the isomer with the phosphonous dichloride group para to methoxyl![22,23]



3h **4h**

The Friedel–Crafts procedure described herein provides a convenient method for the preparation of arylphosphonous dichlorides. A rational prediction of product distribution is also possible. The reaction appears reasonably general for methoxy-substituted aromatic rings which do not contain electron-withdrawing groups.

Experimental Section[24]

General Procedure for Preparation of Arylphosphonous Dichlorides. A. $SnCl_4$ Catalyst. A solution of 0.1 mol of the anisole, 0.30 mol (26 ml, 41 g) of phosphorus trichloride, and 2 ml of anhydrous stannic chloride was refluxed under dry nitrogen for the specified length of time. An extra 1–2 ml of stannic chloride was added every 12–18 hr. The mixture was concentrated under reduced pressure, and the residue was rapidly distilled at high vacuum. The clear oils obtained were redistilled slowly through a 10 in. Vigreux column. Separation of unreacted starting material (if present) and other low-boiling substances was effected near room temperature (0.05–0.3 mm). The desired product was collected at a much higher temperature [80–140° (0.05–0.3 mm)] and was sufficiently pure for elemental analysis.

B. $FeCl_3$ Catalyst. The same ratio of reactants as in (A) was used with 2.0 g of anhydrous ferric chloride instead of stannic chloride. Work-up consisted of filtration of the reaction mixture through Celite after the specified reaction time. The Celite was washed thoroughly with benzene, and the combined filtrates were concentrated under reduced pressure. The residue was vacuum distilled according to procedure A.

The phosphonous dichlorides were converted to the phosphonic acids by adaptation of the method of Amonoo-Nizer, Ray, Shaw, and Smith.[25]

A solution of 0.1 mol of the phosphonous dichloride in 200 ml of methylene chloride was cooled to −70° under nitrogen with mechanical stirring. A solution of 0.1 mol of dimethyl sulfoxide in 50 ml of methylene chloride was added dropwise at such a rate that the temperature remained below −50°. The solution was warmed to room temperature and then concentrated under reduced pressure to leave clear, slightly yellow oils or low-melting solids. These phosphonic dichlorides could be vacuum distilled or merely treated with enough acetone and water to solubilize the product. Heating the solution on the steam bath, followed by slow cooling, gave high (80–90%) overall yields of phosphonic acids. In cases where isomer mixtures were used, the slow rate of cooling was essential to isomer separation.

The phosphinic acids were prepared by treating 1–2 g of phosphonous dichloride with enough water (~10 ml) and acetone to provide a homogeneous solution. Heating the solution on the steam bath was followed by slow cooling to give 60–80% yields of phosphinic acids.

Registry No.—**3a,** 100-66-3; **3b,** 100-68-5; **3c,** 578-58-5; **3d,** 91-16-7; **3e,** 151-10-0; **3f,** 100-84-5; **3g,** 135-77-3; **3h,** 2944-49-2; **3i,** 6738-23-4; **3j,** 5673-07-4; **3k,** 10568-38-4; **3l,** 6380-20-7; **3m,** 33733-83-4; **3n,** 1126-79-0; **3o,** 103-73-1; **3p,** 622-85-5; **4a,** 19909-85-4; **4b,** 53534-47-7; **4c,** 53534-48-8; **4d,** 53534-49-9; **4e,** 53534-50-2; 4-CH_3O-**4f,** 53534-51-3; 2-CH_3O-**4f,** 53534-52-4; **4g,** 53534-53-5; **4h,** 53534-54-6; **4i,** 53534-55-7; **4j,** 53534-56-8; 4-CH_3O-**4k,** 53534-57-9; 2-CH_3O-**4k,** 53534-58-0; 4-CH_3O-**4l,** 53534-59-1; 2-CH_3O-**4l,** 53534-60-4; **4m,** 53534-61-5; **4n,** 53534-64-8; **4o,** 53534-62-6; **4p,** 53534-63-7; **6a,** 53534-65-9; **6b,** 53534-66-0; **6c,** 53534-67-1; **6d,** 53534-68-2; **6e,** 53534-69-3; 4-CH_3O-**6f,** 53534-70-6; 2-CH_3O-**6f,** 53534-71-7; **6h,** 53586-52-0; **6i,** 53534-72-8; **6j,** 53534-73-9; **6m,** 53534-74-0; **7a,** 21778-19-8; **7b,** 46061-42-1; **7c,** 53534-75-1; **7d,** 53534-76-2; **7e,** 53534-77-3; 4-CH_3O-**7f,** 53534-78-4; 2-CH_3O-**7f,** 53534-79-5; **7h,** 53534-80-8; **7j,** 53534-81-9; $SnCl_4$, 7646-78-8; $FeCl_3$, 7705-08-0; PCl_3, 7719-12-2.

References and Notes

(1) For a general literature review of the entire area of phosphonous dichloride chemistry, see G. M. Kosolapoff and L. Maier, "Organic Phosphorus Compounds," Vol. 4, Wiley-Interscience, New York, N.Y., 1972, pp 75–157.

(2) A discussion of the improvements, limitations and problems in this process can be found in: G. M. Kosolapoff, "Friedel Crafts and Related Reactions," Vol. 4, G. Olah, Ed., Wiley-Interscience, New York, N.Y., 1965, pp 213; also see ref 1, p 79–81.

(3) G. M. Kosolapoff, ref 2, pp 222–224.

(4) M. Bourneuf, *Bull. Soc. Chem. Fr.*, **33,** 1808 (1923); L. Benda and. W. Schmidt, U.S. Patent 1607113 (1926); *Chem. Abstr.*, **21,** 249 (1927); H. Randnitz, *Ber.*, **60,** 743 (1927); M. P. Viout, *J. Rech. Cent. Nat. Rech.*, **No. 28,** 15 (1954); *Chem. Abstr.* **50,** 249 7077 (1956).

(5) W. C. Davies and C. J. O. R. Morris, *J. Chem. Soc.*, 2880 (1932).

(6) A. Michaelis, *Justis Liebigs Ann. Chem.*, **294,** 1 (1896); 293, 193 (1896).

(7) P. Kunz, *Ber.*, **27,** 2559 (1894).

(8) I. K. Jackson, W. C. Davies, and W. J. Jones, *J. Chem. Soc.*, 2298 (1930); G. Kamai, *Zh. Obshch. Khim.*, **4,** 192 (1934).

(9) Varying the amounts of $AlCl_3$ had no effect on the outcome of the reaction. Use of a fresh bottle of anhydrous $AlCl_3$ likewise gave only ether cleavage.

(10) G. M. Kosolapoff, ref 2, p 223.

(11) H. S. Mason, *J. Amer. Chem. Soc.*, **69,** 2241 (1947); J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 4435 (1955); G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **25,** 721 (1960).

(12) I. S. Protopopov and M. Ya.Kraft, *Zh. Obshch. Khim.*, **34,** 1446 (1964); **33,** 3050 (1963).

(13) M. P. Viout, *J. Rech. Cent. Nat. Rech.*, **No. 28,** 15 (1954); M. P. Viout and P. Rumpf, *Bull. Soc. Chim. Fr.*, 768 (1957).

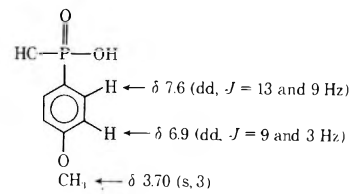
(14) G. M. Kosolapoff, ref 2, p 223.

(15) Stannic chloride has been used as a Friedel–Crafts catalyst for the preparation of 2-thienyl phosphonous dichloride but not for preparation of any benzenoid phosphonous dichlorides. See M. Bentov, L. David, and E. D. Bergman, *J. Chem. Soc.*, 4750 (1963).

(16) Reaction mixtures often precipitated some crystalline, hygroscopic complex, presumably ($SnCl_4$–PCl_3), which could be filtered off without difficulty before product isolation.

(17) In view of the utility of stannic chloride as a catalyst for the reaction under study, another mild, organic soluble catalyst candidate, titanium tetrachloride, was studied in one case. Using the same conditions as those used with stannic chloride, titanium tetrachloride was found to catalyze the conversion of anisole **3a** to *p*-anisyl phosphonous dichloride **4a** in approximately 50% yield after a reaction time of 64 hr.

(18) The nmr spectra of the phosphonous dichlorides, phosphinic acids, and phosphonic acids prepared were very diagnostic in determining patterns of substitution. The $-PCl_2$, $-PO_2H_2$, and $-PO_3H_2$ groups are all strongly deshielding, and protons ortho to them were found between δ 7.5 and 8.0, a full ppm lower field than protons ortho to methoxyl, methyl, or hydrogen. Coupling constants between ring protons and phosphorus did not follow a consistent pattern, apparently altered by steric and electronic factors; however, coupling between ortho and meta protons and phosphorus was routinely observed. No coupling between para protons and phosphorus could be seen. Proton–proton ring coupling constants were normal, 8–10 Hz for ortho and 1–3 Hz for meta. For example, *p*-anisylphosphonic acid gave a completely interpretable spectrum.



(19) E. H. Amonoo-Nizer, S. K. Ray, R. A. Shaw, and B. B. Smith, *J. Chem. Soc.*, 4296 (1965).

(20) Although unusual in aromatic electrophilic substitutions, complete specificity for para substitution is known. The Friedel–Crafts acetylation of anisole with aluminum chloride has been shown to give exclusively para substitution. See L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1,** 61 (1963).

(21) In addition, *p*-dimethoxybenzene or *p*-methylanisole both failed to react under the reaction conditions.

(22) That the isomer formed was correctly identified was shown by comparison of its nmr spectrum with that of the isomeric mixtures of phosphonous dichlorides from *m*-methylanisole, *m*-isopropylanisole, and the single isomer obtained from *m*-*tert*-butylanisole.

(23) A further unexpected result came from the observation that 1,2,3-trimethoxybenzene failed to react at all under the conditions employed, while 3-methyl veratrole gave primarily ether cleavage to the aryl di-$OPCl_2$ product. A rationale for the abnormal reactivities of certain anisoles studied is not clear. However, it probably involves steric inhibition of resonance in the polysubstituted anisoles, especially those in which ring substituents are in consecutive positions. See, for instance, L. M. Stock, "Aromatic Substitution Reactions," K. L. Rinehart, Ed., Prentice-Hall, Englewood Cliffs, N.J. 1968, pp 54–55.

(24) Nmr spectra were recorded on a Varian Model T-60 or EM-360 spectrometer in CC_4 or $CDCl_3$ for the phosphonous dichiorides and DMSO-d_6 for the phosphinic and phosphonic acids with tetramethyisilane (TMS) as the internal standard. The chemical shifts are reported in ppm (δ). All boiling points and melting points are uncorrected. Melting points were determined on a Mel-Temp apparatus. Elemental analyses were determined by Atlantic Microlabs, Atlanta, Georgia. Most of the anisoles were commercially available. Those that were not were prepared by alkylation of the corresponding phenols according to the procedure of G. N. Vyas and N. M. Shah, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 837.

(25) E. H. Amonoo-Nizer, S. K. Ray, R. A. Shaw, and B. B. Smith, *J. Chem. Soc.*, 4296 (1965).

Synthesis of 5,8,11-Dodecatriynoic Acid and Its Use in the Synthesis of Arachidonic Acid and Related Acids

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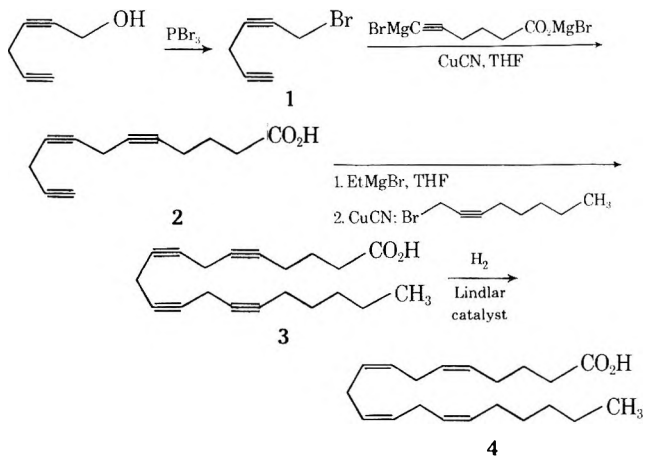
The preparation of 5,8,11-dodecatriynoic acid *via* a Grignard coupling of 1-bromo-2,5-hexadiyne and 5-hexynoic acid is described. The triynoic acid has been used as an intermediate in a new synthesis of arachidonic acid and of novel methyl-branched arachidonic acids.

The standard approach for the synthesis of arachidonic acid, *all-cis*-5,8,11,14-eicosatetraenoic acid (**4**), has been the preparation of long-chain polyacetylenic compounds followed by the selective hydrogenation of the acetylenic bonds to cis olefins. Two variations, among others, of this approach which have been adopted for the synthesis of arachidonic acid involve (a) the coupling of a C_{10} and a C_9 fragment[1] and (b) the coupling of a C_{14} and a C_6 fragment.[3-5]

We now wish to report a new synthesis of arachidonic acid which involves the coupling of a C_8 fragment with a novel C_{12} fragment, 5,8,11-dodecatriynoic acid (**2**).

The C_{12} acid **2** was prepared by bromination of 2,5-hexadiyn-1-ol[6] with phosphorus tribromide to give 1-bromo-2,5-hexadiyne (**1**) which was then coupled with 5-hexynoic acid in the presence of ethylmagnesium bromide and cuprous ion (see Scheme I). The acid **2** was then coupled with

Scheme I



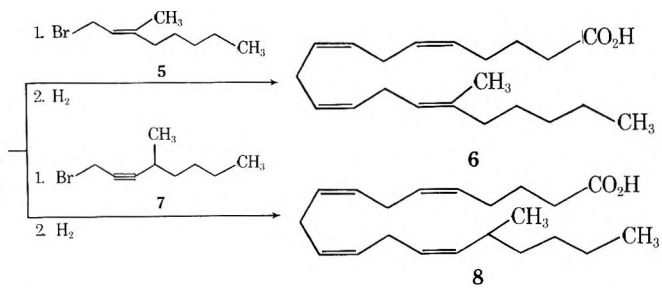
the C_8 fragment, 1-bromo-2-octyne,[7] under the same Grignard conditions, to give 5,8,11,14-eicosatetraynoic acid (**3**) which was selectively reduced to arachidonic acid (**4**), according to literature procedures.[3]

The triynoic acid **2**, which is very sensitive to air oxidation, was purified by low-temperature recrystallization and can be stored for several months at −40° when kept in an inert (argon) atmosphere.

The intermediate **2** has also been used for the preparation of 15-methyl- and 16-methylarachidonic acids, compounds **6** and **8** respectively, two novel alkyl-branched fatty acids (see Scheme II).

The allylic bromide **5** was prepared by bromination of *cis*- and *trans*-3-methyl-2-octen-1-ol[8] with phosphorus tribromide. The acetylenic bromide **7** was prepared by the hydroxyalkalation of 3-methyl-1-heptyne[9] followed by bromination with phosphorus tribromide.

Scheme II



These two bromo compounds were individually coupled with **2** under the Grignard conditions described above to give polyacetylenic intermediates, which were extremely unstable and difficult to purify. The crude acetylenic products were treated with silver nitrate in aqueous ethanol to remove excess acid **2**, followed by recrystallization at −10° to give unstable, low-melting solids. The nmr spectra of these acetylenic acids were consistent with the assigned structures. These partially purified acids were immediately hydrogenated over Lindlar catalyst to the tetraenoic acids **6** and **8** which were easily purified by column chromatography.

The 15-methyl acid **6** was obtained as a mixture of cis–trans isomers at the C_{14} double bond. The original alcohol, 3-methyl-2-octen-1-ol,[8] was obtained as a 4:1 trans:cis isomeric mixture and the final tetraenoic acid **6** was assumed to have predominantly the trans configuration at the 14–15 double bond, although this point was not conclusively proven.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. The ir spectra were recorded with either a Beckman IR-9 or a Perkin-Elmer 137 spectrophotometer. The nmr spectra were recorded with a Varian T60, A-60, or HA-100 instrument in deuteriochloroform. Absorption peaks are recorded in parts per million downfield from an internal standard (TMS). All reactions were carried out under argon. All Grignard reagents were prepared immediately before use and were standardized by titration.

1-Bromo-2,5-hexadiyne (1). To a solution of 10.9 g (116 mmol) of crude 2,5-hexadiyn-1-ol[6] in 175 ml of ether (cooled to 5°) was added, *via* syringe, 4.35 ml (12.4 g, 46 mmol) of phosphorus tribromide (PBr_3). The mixture was stirred at 3–10° for 6 hr. After pouring into ice water, the aqueous phase was extracted well with ether. The ether extracts were combined, washed with saturated bicarbonate, brine, dried (Na_2SO_4), concentrated, and distilled (cautiously) through a short-path column to yield 9.6 g (53%) of **1** as a colorless oil, bp 40–43° (0.3 mm). The compound darkens rapidly and should be used as soon as possible after distillation: ir (neat) 3240 (C≡CH) 1405, 1310, 1210 cm^{-1} (no absorption due to OH); nmr δ 2.12 (t, 1 H, C≡CH), 3.52 (q, 2 H, C≡CCH_2C≡C), 3.93 (t, 2 H, CH_2Br).

5,8,11-Dodecatriynoic Acid (2). To a solution of 10.98 g (98 mmol) of 5-hexynoic acid in 100 ml of THF, cooled to 5°, was

added dropwise 116 ml (196 mmol) of a 1.69 *M* solution of ethylmagnesium bromide in THF. The solution was allowed to warm to room temperature over 1 hr and 500 mg of cuprous cyanide (CuCN) was added. After stirring 20 min, a solution of 7.7 g (49 mmol) of **1** in 40 ml of THF was added dropwise over 30 min. The reaction was stirred for 5 hr at room temperature and an additional 500 mg of CuCN was added. After stirring for a total of 22 hr, the mixture was poured into 300 ml of 3 *N* H_2SO_4 and 100 g of ice. After extraction with ether, the organic phase was concentrated *in vacuo*. The residue was dissolved in ether and the ether solution washed with Versene[10] several times to remove copper, washed with water, dried ($MgSO_4$), and concentrated to yield a brown oil. The oil was dissolved in a mixture of ether and petroleum ether (bp 30–60°) and stored overnight at −40°. The crystalline product was recrystallized three times at −30° from ether–petroleum ether to yield 3.0 g (30%) of **2**, mp 51–53°. The triynoic acid was sensitive to air as judged by coloration and lowering of melting points. An analytical sample was prepared by recrystallization from hexane at −15° to give beige plates: mp 57–58°; ir (KBr) 3295, 3285 (C≡CH), 1710, 1690 (C=O), 920 cm^{-1}; nmr δ 1.80 (m, 2 H, $CH_2CH_2CH_2$), 2.07 (t, 1 H, C≡CH), 2.25 (dist. t, 2 H, C≡CCH_2CH_2), 2.47 (t, 2 H, CH_2C=O), 3.13 (m, 4 H, C≡CCH_2C≡CCH_2C≡C), 10.77 (s, 1 H, CO_2H).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.58; H, 6.43. Found: C, 76.43; H, 6.61.

5,8,11,14-Eicosatetraynoic Acid (3). To a solution of 3.95 g (21 mmol) of **2** in 30 ml of THF at 3° was added dropwise 37.2 ml (42 mmol) of a 1.13 *M* solution of ethylmagnesium bromide in THF. The mixture was stirred at room temperature for 1.5 hr and 150 mg of CuCN added. After stirring for 20 min, 2.65 g (14 mmol) of 1-bromo-2-octyne[7] was added and rinsed in with 5 ml of THF. The mixture was then stirred for 18 hr with an additional 150 mg of CuCN added after 6 hr. The product was isolated in the same manner as that described for **2**, and was recrystallized from isopropyl alcohol to give 2.70 g (64%) of **3**. An analytical sample was prepared by recrystallization from *i*-PrOH at −10°. The acid was obtained as beige plates: mp 80.5–82° (lit.[3b] mp 81–82°); ir ($CHCl_3$) 3400–2500 (broad OH), 1715; nmr δ 0.90 (dist. t, 3 H, CH_3), 1.38 (br m, 6 H, $(CH_2)_3CH_3$), 1.85 (m, 2 H, CH_2CH_2C=O), 2.03–2.37 (br m, 4 H, CH_2CH_2C≡C), 2.49 (t, 2 H, CH_2CO_2), 3.15 (m, 6 H, C≡CCH_2C≡C), 10.85 (s, 1 H, CO_2H).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.18; H, 8.25.

1-Bromo-3-methyl-*cis,trans*-2-octene (5). To a solution of 19.0 g (135 mmol) of 3-methyl-*cis,trans*-2-octen-1-ol[8] in 400 ml of ether, cooled to 5°, was added, *via* syringe, 9.8 ml (14.3 g, 53 mmol) of PBr_3. The reaction was stirred at 3–10° for 5 hr, and the product isolated following the procedure given for **1**. Distillation of the crude product yielded 19.6 g (71%) of **5** as a colorless oil: bp 50.5–51.5° (0.7 mm); ir (neat) 1605, 1460, 1375, 1205 cm^{-1} (no absorption due to OH); nmr δ 0.90 (dist. t, 3 H, CH_3CH_2), 1.30 (br m, 6 H, $CH_2CH_2CH_2$), 1.70 (d, 3 H, CH_3C=C, *J* = 2 Hz), 2.03 (dist. t, 2 H, CH_2C=C), 4.00 (d, 2 H, CH_2Br), 5.50 (t, 1 H, C=CH).

Anal. Calcd for $C_9H_{17}Br$: C, 52.70; H, 8.35. Found: C, 53.03; H, 8.30.

15-Methyl-14-*cis,trans*-eicosaen-5,8,11-triynoic Acid. To a solution of 12.4 g (66 mmol) of **2** in 120 ml of THF, cooled to 0°, was added dropwise 132 ml (132 mmol) of a 1.0 *M* solution of ethylmagnesium bromide in THF. The mixture was warmed to room temperature and stirred for 4.5 hr and then 400 mg of CuCN was added. After stirring 20 min, a solution of 9.02 g of **5** in 50 ml of THF was added dropwise. The mixture was then stirred for 17 hr, with an additional 400 mg of CuCN added after 6 hr. The reaction was worked up as described for **2** to give 20.5 g of crude product. The crude product was dissolved in 60 ml of absolute EtOH and added to a solution of 22 g of $AgNO_3$ dissolved in 25 ml of H_2O and 225 ml of absolute EtOH to precipitate the silver salt of **2**. The mixture was filtered through Hyflo and the filtrate was diluted with an equal volume of water and extracted twice with a 1:1 mixture of ether–pentane. The combined organic extracts were washed three times with water, once with brine, dried ($MgSO_4$), and concentrated to give 12.5 g of orange oil. The oil dissolved in pentane and recrystallized at −10°. The product was filtered quickly through a prechilled funnel and recrystallized from ether–pentane at 5° to give 3.8 g of a gummy yellow solid (low melting) which was dried under high vacuum. The product should be stored under argon at −40° to prevent decomposition. The product was too unstable to obtain a satisfactory elemental analysis: ir (neat) 3500–2400 (br OH), 1710 (C=O), 1410 cm^{-1}; nmr δ 0.89 (dist. t, 3 H, CH_3CH_2), 1.45 (br m, 6 H, $CH_2CH_2CH_2CH_3$), 1.60 (s, 3 H, CH_3C=C), 1.85–2.68 (m, 8 H, $CH_2CH_2CH_2CO_2$, CH_2C=C), 2.88 (d, 2 H, C=CHCH_2C≡C), 3.13 (t, 4 H, C≡CCH_2C≡CCH_2C≡C, *J* = 2 Hz), 5.02 (t, 1 H, olefin proton).

15-Methyl-5,8,11-*cis*-14-*cis,trans*-eicosatetraenoic Acid (6). To a solution of 870 mg (2.7 mmol) of 15-methyl-14-*cis,trans*-eicosaen-5,8,11-triynoic acid in 25 ml of absolute EtOH was added 300 mg of Lindlar catalyst followed by 0.1 ml of quinoline. Immediately, the mixture was reduced under a slight positive pressure of hydrogen. The reaction took up 213 ml of H_2 in 7500 sec; theoretical uptake (corrected), 206 ml. The mixture was filtered through hyflo and concentrated *in vacuo*. The residue was dissolved in ether, washed with cold 1 *N* HCl, brine, dried ($MgSO_4$), and concentrated to give 827 mg of crude product as a gold colored oil. Chromatography on a 21 × 1.3 cm column of silica gel, using ether in hexane (the percentage of ether was gradually increased from 0 to 16%) as eluent, gave 689 mg (79%) of **6** as a lightly colored oil. A small amount was rechromatographed to give the analytical sample: ir (neat) 3550–2550 (br OH), 1710 (C=O) cm^{-1}; nmr δ 0.87 (dist. t, 3 H, CH_2CH_3), 1.26 (br m, 6 H, $CH_2CH_2CH_2CH_3$), 1.60 (s, 3 H, CH_3C=C), 1.69 (t, 2 H, $CH_2CH_2CO_2$), 2.02 (m, 4 H, CH_2C=C, C=CHCH_2CH_2), 2.35 (t, 2 H, CH_2CO_2), 2.81 (br m, 6 H, 3 × C=CCH_2C=C), 5.09 (t, 1 H, CH_3C=C*H*), 5.35 (m, 6 H, 3 × CH=CH), 10.5 (br s, 1 H, CO_2H).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.81; H, 10.51.

4-Methyl-2-octyn-1-ol. To a solution of 28.g (254 mmol) of 3-methyl-1-heptyne[9] in 1 l. of THF, cooled to 0°, was added dropwise 145 ml (230 mmol) of a 1.6 *M* solution of *n*-butyllithium in hexane. After stirring for 45 min, 10.5 g (350 mmol) of *p*-formaldehyde (dried over P_2O_5) was added. The reaction was stirred for 1 hr at room temperature, heated to 45–50° for 3 hr, cooled, and concentrated *in vacuo* to a volume of 300 ml. The concentrated solution was poured into 1200 ml of saturated NH_4Cl solution and extracted with ether. The ether extract was washed with saturated NH_4Cl, dried ($MgSO_4$), and concentrated. Distillation of the crude product gave 17.6 g (50%) of 4-methyl-2-octyn-1-ol as a colorless oil: bp 59–62° (0.3 mm); ir ($CHCl_3$) 3615 (free OH), 3700–3250 (bonded OH), 2240 (C≡C), 1460, 1380 cm^{-1}; nmr δ 0.91 (dist. t, 3 H, CH_2CH_3), 1.15 (d, 3 H, $CHCH_3$), 1.43 (br m, 6 H, $CH_2CH_2CH_2$), 2.07 (br s, 1 H, OH), 2.18–2.60 (br m, 1 H, CHC≡C), 4.76 (s, 2 H, CH_2OH).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.23; 76.38; H, 11.51, 11.50.

1-Bromo-4-methyl-2-octyne (7). To a solution of 17.6 g (127 mmol) of 4-methyl-2-octyn-1-ol in 200 ml of ether, cooled to 5°, was added, *via* syringe, 4.7 ml (13.8 g, 51 mmol) of PBr_3. After stirring at 3–10° for 5.5 hr, the product was isolated following the procedure given for the isolation of **1**. Distillation of the crude product gave 13.73 g (57%) of **7**, as a colorless oil: bp 45–46° (0.35 mm); ir (neat) 2240 (C≡C), 1460, 1210, 610 (CBr) cm^{-1} (no absorption due to OH); nmr δ 0.91 (dist. t, 3 H, CH_3), 1.13 (d, 3 H, CH_3CH), 1.40 (br m, 6 H, $CH_2CH_2CH_2$), 2.42 (br m, 1 H, CH), 3.93 (s, 2 H, CH_2Br).

Anal. Calcd for $C_9H_{15}Br$: C, 53.22; H, 7.44. Found: C, 52.97; H, 7.34.

16-Methyl-5,8,11,14-eicosatetraynoic Acid. To a solution of 11.2 g (59.5 mmol) of **2** in 110 ml of THF, cooled to 0°, was added 120 ml (119 mmol) of a 0.99 *M* solution of ethylmagnesium bromide in THF. After warming to room temperature, the mixture was stirred for 4 hr, and then 350 mg of CuCN was added. After stirring 20 min, a solution of 6.91 g (34 mmol) of **7** in 45 ml of THF was added dropwise. The mixture was stirred for 17 hr with an additional 350 mg of CuCN added after 6 hr. The reaction was then worked up in the manner described for **2** to give 17.7 g of crude product, which was treated with 20 g of $AgNO_3$ as described above for the 15-methylenetriynoic acid. The crude product which was obtained was recrystallized from ether–pentane to give 4.6 g (44%) of 16-methyl-5,8,11,14-eicosatetraynoic acid, as a low-melting, unstable solid. The product was hydrogenated as soon as possible after isolation to avoid decomposition: ir (neat) 3500–2550 (br OH), 1710 (C=O), 1400 cm^{-1}; nmr δ 0.91 (dist. t, 3 H, CH_2CH_3), 1.13 (d, 3 H, CH_3CH), 1.40 (br m, 6 H, $CH_2CH_2CH_2$), 1.87 (q, 2 H, $CH_2CH_2CO_2$), 2.07–2.70 (m, 5 H, $CH_2CH_2CH_2CO_2$, CHC≡C), 10.97 (s, 1 H, OH).

16-Methyl-5,8,11,14-eicosatetraenoic Acid (8). To a solution of 670 mg (2.13 mmol) of 16-methyl-5,8,11,14-eicosatetraynoic acid in 15 ml of absolute EtOH was added 650 mg of Lindlar catalyst and 0.20 ml of quinoline. Immediately, the mixture was reduced under a slight positive pressure of hydrogen. The reaction took up 188 ml of hydrogen in 6800 sec; theoretical uptake (cor-

rected), 230 ml. Following the procedure given for the purification of **6**, 340 mg (53%) of **8** was obtained as a lightly colored oil, after chromatography. A small amount was rechromatographed to give the analytical sample: ir (neat) 3450–2450 (broad OH), 1690 (C=O) cm^{-1}; nmr δ 0.88 (dist. t, 3 H, CH_2CH_3), 0.94 (d, 3 H, $CHCH_3$), 1.27 (br m, 6 H, 3 × CH_2), 1.72 (q, 2 H, $CH_2CH_2CO_2$), 2.12 (t, 2 H, $C{=}CCH_2CH_2$), 2.20 (br s, 1 H, CHC=C), 2.38 (t, 2 H, CH_2CO_2), 2.82 (br m, 6 H, 3 × $C{=}CCH_2C{=}C$), 5.06–5.46 (m, 8 H, 4 × CH=CH), 11.15 (br s, 1 H, CO_2H).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.09; H, 10.96.

Acknowledgment. We are indebted to the following members of our Physical Chemistry Department under the direction of Dr. R. P. W. Scott: Dr. F. Scheidl for elemental analyses, Dr. T. Williams for nmr spectra, and Mr. S. Traiman for ir spectra.

Registry No.—**1**, 20334-69-4; **2**, 53292-96-9; **3**, 1191-85-1; **4**, 506-32-1; *cis*-**5**, 53369-62-3; *trans*-**5**, 53292-97-0; 14-*cis*-**6**, 53292-98-1; 14-*trans*-**6**, 53368-42-6; **7**, 53292-99-2; **8**, 53319-93-0; 2,5-hexadiyn-1-ol, 28255-99-4; phosphorus tribromide, 7789-60-8; 5-hexynoic acid, 53293-00-8; ethyl bromide, 74-96-4; 3-methyl-*cis*-2-octen-1-ol, 30804-78-5; 3-methyl-*trans*-2-octen-1-ol, 30804-71-8; 15-methyl-14-*cis*-eicosaen-5,8,11-triynoic acid, 53293-01-9; 15-methyl-14-*trans*-eicosaen-5,8,11-triynoic acid, 53293-02-0; 4-methyl-2-octyn-1-ol, 53369-63-4; 3-methyl-1-heptyne, 53293-03-1; 16-methyl-5,8,11,14-eicosatetraynoic acid, 53293-04-2.

References and Notes

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(10) The versene solution was prepared by mixing 100 g of Versene 100 (obtained from Fisher Scientific Co.), 500 ml of H_2O, and 20 ml of 37% hydrochloric acid.

Synthesis of Di- and Tripeptides Containing 4-Aminocyclohexanecarboxylic Acid

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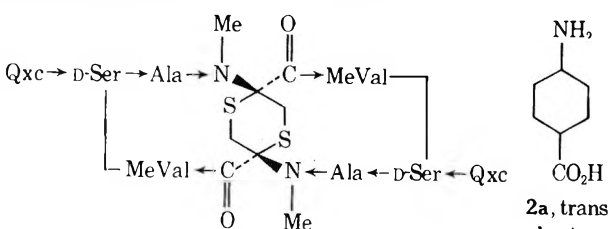
Studies of selected coupling methods for attachment of amino acid derivatives to *cis*- and *trans*-4-aminocyclohexanecarboxylic acid have shown diethylphosphoryl cyanide to be an effective coupling reagent. *N-tert*-Butyloxycarbonyl-*trans*-4-aminocyclohexanecarboxylic acid (**3a**) was converted, using diethylphosphoryl cyanide, to dipeptide **4a** by condensation with L-valine methyl ester. Dipeptide **4a** was transformed by deprotection and coupling with *N-tert*-butyloxycarbonyl-L-alanine to tripeptide **6a**. Similar transformations were effected using the *N-tert*-butyloxycarbonyl derivative **3b** of *cis*-4-aminocyclohexanecarboxylic acid. Other coupling procedures investigated were the carbodiimide, *p*-nitrophenyl active ester, and symmetrical anhydride methods; these methods were less satisfactory for effecting coupling to the above cyclohexaneamino acids.

The quinomycins[1] are a group of depsipeptide antibiotics that possess a depsipeptide lactone system interconnected by a 1,4-dithiane ring as shown for echinomycin (**1**). Our interest in the synthesis of quinomycin model systems that have a cyclohexane ring substituted for the dithiane moiety has resulted in an investigation of methods for attachment of amino acid derivatives to the simple model 4-aminocyclohexanecarboxylic acid (**2**).



1, Qxc = 2-quinoxalinecarbonyl

2a, trans
b, cis

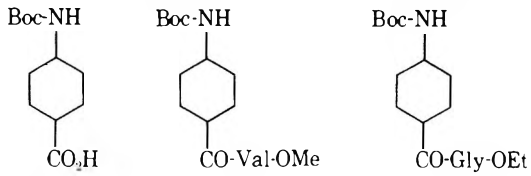
Interest in the preparation of peptide derivatives of 1-aminocyclopentane- and 1-aminocyclohexanecarboxylic acids was prompted by the reported[2] cytotoxic activity of the former substance. Amino acid derivatives were attached to the above cycloalkylamino acids by application of the acid chloride,[3a] carbodiimide,[3a–c] symmetrical anhydride,[3d] and oxazolone[3d] methods. Amino acids also have been attached to cyclohexylamine by use of active esters.[4]

In this study, *trans*-4-aminocyclohexanecarboxylic acid (**2a**)[5] was chosen as an appropriate model, since in the quinomycins the dithiane amino acid moiety has, in the 2,5 positions, amino and carboxyl groups in a trans relationship; studies were made also on the corresponding cis isomer **2b**. Conversion of **2** to the *N-tert*-butyloxycarbonyl derivative **3** was effected by standard procedures.[6] Initial attempts to couple glycine ethyl ester or L-alanine methyl ester to **3** using *N,N'*-dicyclohexylcarbodiimide[7] with or without added 1-hydroxybenzotriazole[8] were not successful. Similar failures employing the carbodiimide method in coupling reactions with cycloalkylamino acids have been observed.[3d,9]

Diethylphosphoryl cyanide recently has been shown[9] to be an effective coupling agent in peptide synthesis. Of significance, condensation of cyclohexylamine with benzoic acid was reported to give *N*-cyclohexylbenzamide in good yield using diethylphosphoryl cyanide, while none of the desired amide was obtained by the carbodiimide method.

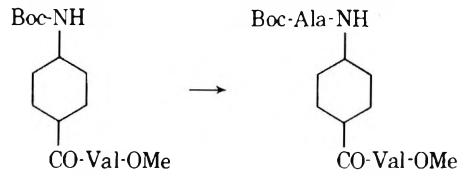
Treatment of *N-tert*-butyloxycarbonyl-*trans*-4-aminocyclohexanecarboxylic acid **3a** with L-valine methyl ester and diethylphosphoryl cyanide in dimethylformamide gave

dipeptide **4a** in 67% yield. In a similar manner, *N-tert*-butyloxycarbonyl-*cis*-4-aminocyclohexanecarbonyl-L-valine methyl ester (**4b**) was prepared in a yield of 64% from **3b**. Glycine ethyl ester was coupled to the cis isomer **3b** to give dipeptide **5** in a yield of 56% using the above method.



3a, trans **4a**, trans **5**
b, cis b, cis

Removal of the *N-tert*-butyloxycarbonyl group in dipeptides **4a** or **4b** with trifluoroacetic acid and subsequent coupling of *N-tert*-butyloxycarbonyl-L-alanine to the cyclohexyl amino group, using diethylphosphoryl cyanide, gave tripeptides **6a** and **6b** in yields of 44 and 47%, respectively.



4a, trans **6a**, trans
b, cis b, cis

Tripeptide **6a** thus represents a cyclohexane model of the tripeptide sequence containing the dithiane moiety present in the quinomycins.

Limited studies on application of the *p*-nitrophenyl active ester method[10] and the symmetrical anhydride method[3d] for attachment of amino acid derivatives to **3** have shown the above methods to be unpromising. Thus, the *p*-nitrophenyl ester of **3b** was observed not to couple to any appreciable extent with glycine ethyl ester in dimethylformamide. Addition of imidazole[4] to the reaction mixture caused reaction to occur; however, dipeptide **5** was obtained in a yield of only 20%. In the second method studied, reaction of **3b** with pivaloyl chloride gave the corresponding symmetrical anhydride[11] of **3b**, which upon reaction with L-valine methyl ester gave dipeptide **4b** in 10% overall yield. Efforts to maximize the yields obtained by the above two methods were not pursued further.

This study establishes that diethylphosphoryl cyanide is the reagent of choice for the attachment of amino acid derivatives to *cis*- or *trans*-4-aminocyclohexanecarboxylic acid. Further studies on the preparation of quinomycin model systems containing the above cyclohexane amino acids are underway.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-20A spectrophotometer. Nmr data were obtained with a Varian A-60 or XL-100 nmr spectrometer. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometrometer. Tlc data were measured on Brinkmann precoated silica gel plates in chloroform–methanol–acetic acid (85:10:5). Evaporations *in vacuo* were carried out with a Buchler rotary evaporator. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich.

***N-tert*-Butyloxycarbonyl-*trans*-4-aminocyclohexanecarboxylic Acid (3a).** To a solution of 1.43 g (10 mmol) of *trans*-4-aminocyclohexanecarboxylic acid[5] and 0.80 g (20 mmol) of magnesium oxide in 30 ml of dioxane–water (1:1) was added 2.15 g (15 mmol) of *tert*-butyloxycarbonyl azide and the mixture was stirred at 45° overnight. Magnesium oxide was removed by filtration and washed with 50 ml of water. The filtrate was extracted with ether (3 × 25 ml), acidified with solid citric acid at 0°, and extracted with ethyl acetate (3 × 30 ml). The ethyl acetate solution was dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from ethyl acetate–petroleum ether (bp 60–90°) to give 1.56 g of white crystals (64%): mp 147–150°; nmr ($CDCl_3$) δ 3.5 (br s, cyclohexyl H_4), 2.6–1.5 (m, cyclohexyl except H_4), 1.45 (s, *tert*-butyl).

Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.2; H, 8.71; N, 5.76. Found: C, 59.18; H, 8.84; N, 5.57.

***N-tert*-Butyloxycarbonyl-*cis*-4-aminocyclohexanecarboxylic Acid (3b).** A solution of 2.86 g (20 mmol) of *cis*-4-aminocyclohexanecarboxylic acid[5] was treated as above for **3a** to give 3.95 g of white solid (81%), mp 163–168°. The solid was recrystallized from ethyl acetate: mp 167–169°; nmr (DMSO-d_6) δ 6.65 (d, 1 H, NH), 3.35 (s, 1 H, cyclohexyl H_4), 2.4 (s, 1 H, cyclohexyl H_1), 2.0–1.2 (m, 17 H, cyclohexyl except H_1 and H_4 and *tert*-butyl).

Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.2; H, 8.71; N, 5.76. Found: C, 59.40; H, 8.66; N, 5.66.

***N-tert*-Butyloxycarbonyl-*trans*-4-aminocyclohexanecarbonyl-L-valine Methyl Ester (4a).** To an ice-cold solution of 0.98 g (4.0 mmol) of *N-tert*-butyloxycarbonyl-*trans*-4-aminocyclohexanecarboxylic acid and 0.86 g (4.4 mol) of L-valine methyl ester hydrochloride in 10 ml of dimethylformamide was added 0.72 g (4.4 mol) of diethylphosphoryl cyanide[9] and 0.84 g (8.4 mmol) of triethylamine. The reaction mixture was stirred for 1 hr at 0° and for 3 hr at room temperature. The solution was diluted with water and extracted with ethyl acetate. The ethyl acetate extract was washed with 10% sodium bicarbonate, 10% citric acid, and water and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to give 0.95 g (67%) of while solid: mp 183–186°; R_f 0.51; $[\alpha]^{21}D$ −15.4° (c 1.8, ethanol); nmr ($CDCl_3$) δ 6.05 (m, NH), 4.55 (m, NH and α-H, 2 H), 3.72 (s, OCH_3, 3 H), 3.40 (m, cyclohexyl H_4, 1 H), 2.5–1.1 (m, cyclohexyl protons, valyl methine), 1.45 (s, *tert*-butyl), 0.9 (q, valyl isopropyl), last three peaks integrated to 24 protons. An analytical sample was prepared by recrystallization from ethyl acetate–petroleum ether (bp 60–90°): mp 185.5–187.5°.

Anal. Calcd for $C_{18}H_{32}N_2O_4$ (356.4): C, 60.7; H, 9.03; N, 7.85. Found: C, 60.6; H, 8.81, N, 7.52.

***N-tert*-Butyloxycarbonyl-*cis*-4-aminocyclohexanecarbonyl-L-valine Methyl Ester (4b). (a) Diethylphosphoryl Cyanide Method.** To an ice-cold solution of 0.98 g (4.0 mmol) of *N-tert*-butyloxycarbonyl-*cis*-4-aminocyclohexanecarboxylic acid and 0.86 g (4.4 mmol) of L-valine methyl ester hydrochloride in 10 ml of dimethylformamide were added 0.72 g (4.4 mmol) of diethylphosphoryl cyanide[9] and 0.84 g (8.4 mmol) of triethylamine. The reaction mixture was stirred for 1 hr at 0° and for 3 hr at room temperature. The solution was diluted with 10 ml of water and extracted with ethyl acetate (3 × 10 ml). The ethyl acetate solution was washed with 10% sodium bicarbonate, water, 10% citric acid, and water and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to give 1.13 g of white solid. The white solid was recrystallized from ethyl acetate–petroleum ether to afford 0.91 g (64%) of white crystals: mp 129–131°; R_f 0.78; $[\alpha]^{21}D$ −10.6° (c 2, DMF); nmr ($CDCl_3$) δ 6.4 (d, 1 H, N-H), 4.9 (d, 1 H, NH), 4.8 (m, 1 H, α-hydrogen), 3.7 (m, 4 H, *O*-methyl, cyclohexyl H_4), 2.5–1.5 (m, 10 H, cyclohexyl except H_4, valyl methine), 1.45 (s, 9 H, *tert*-butyl), 0.9 (q, 6 H, valyl nonequivalent isopropyl).

Anal. Calcd for $C_{17}H_{32}N_2O_4$: C, 60.6, H, 9.05; N, 7.86. Found: C, 60.6; H, 9.25; N, 7.76.

(b) Symmetrical Anhydride Method. A stirred and cooled solution of 0.98 g (4.0 mmol) of *tert*-butyloxycarbonyl-*cis*-4-aminocyclohexanecarboxylic acid and 0.40 g (4.0 mmol) of triethylamine in dry benzene was treated with 0.48 g (4.0 mmol) of pivaloyl chloride. The solution was stirred at 0° for 2 hr and then stirred overnight at room temperature. The solution was filtered and the filtrate was evaporated under reduced pressure. Petroleum ether (bp 30–60°) was added and the solution was allowed to stand in a refrigerator for 3 days. A solid (0.51 g) was collected by filtration; an nmr spectrum showed this material to be the symmetrical anhydride. This solid, which did show a second minor spot in tlc, was not further purified for use in the next step of the reaction.

To an ice-cold mixture of 0.18 g (1.1 mmol) of L-valine methyl ester hydrochloride and 0.12 g of triethylamine in benzene was added the above anhydride. The reaction mixture was stirred at 0° for 1 hr and at room temperature overnight. The solvent was removed *in vacuo* and the residue was triturated with 10% sodium bicarbonate, 10% citric acid, and water to give 0.15 g (yield 10%) of **4b**, mp 131–132°.

***N-tert*-Butyloxycarbonyl-*cis*-4-aminocyclohexanecarbonylglycine Ethyl Ester (5).** To a precooled solution of 0.49 g (2.0 mmol) of *N-tert*-butyloxycarbonyl-*cis*-4-aminocyclohexanecarb-

oxylic acid in 10 ml of dimethylformamide were added 0.36 (2.2 mmol) of diethylphosphoryl cyanide, 0.31 g (2.2 mmol) of glycine ethyl ester hydrochloride, and 0.42 g (4.2 mmol) of triethylamine. The reaction mixture was stirred for 1 hr at 0° and 3 hr at room temperature. The solution was diluted with 10 ml of water and extracted with ethyl acetate (2 × 10 ml). The ethyl acetate solution was washed with 10% sodium bicarbonate, water, 10% citric acid, and water and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to give 0.57 g of an oil. The oil was crystallized from ether–petroleum ether (bp 60–90°) to give 0.36 g (56%) of white crystals: mp 224–226°; R_f 0.77; nmr ($CDCl_3$) δ 6.9 (m, 1 H, NH), 5.05 (d, 1 H, NH), 4.2 (q, 2 H, ethyl ester methylene), 3.95 (d, 2 H, α-hydrogens), 3.7 (br s, 1 H, cyclohexyl H_4), 2.5–0.9 (m, 21 H, cyclohexyl except H_4, *tert*-butyl, and ethyl ester methyl).

Anal. Calcd for $C_{16}H_{28}N_2O_5$: C, 58.5; H, 8.59; N, 8.53. Found: C, 58.6; H, 8.49; N, 8.37.

Attempts to prepare **5** using the *N,N'*-dicyclohexylcarbodiimide–1-hydroxybenzotriazole method[8] were unsuccessful.

***N-tert*-Butyloxycarbonyl-L-alanyl-*trans*-4-aminocyclohexanecarbonyl-L-valine Methyl Ester (6a).** *N-tert*-Butyloxycarbonyl-*trans*-4-aminocyclohexanecarbonyl-L-valine methyl ester (0.89 g, 2.5 mmol) was dissolved in 5 ml of trifluoroacetic acid. After 1 hr, the solvent was removed *in vacuo*. To the residue was added 5 ml of dimethylformamide, 0.27 g (2.7 mmol) of triethylamine, and 0.48 g (2.48 mmol) of *N-tert*-butyloxycarbonyl-L-alanine. The solution was cooled to 0° and 0.42 g (2.58 mmol) of diethylphosphoryl cyanide and 0.27 g (2.7 mmol) of triethylamine were added. The reaction mixture was stirred for 1 hr at 0° and overnight at room temperature. The solution was diluted with water and extracted with ethyl acetate. The organic phase was washed with 10% $NaHCO_3$, water, and 10% citric acid. The ethyl acetate was removed *in vacuo* to give 0.64 g of a white solid which was recrystallized from ethyl acetate–ether to give 0.47 g (44%) of **6a**: mp 216–218°; R_f 0.57; $[\alpha]^{21}D$ −33.5° (*c* 1.5, ethanol); nmr ($CDCl_3$) δ 6.35 (m, 2 H, NH), 5.3 (d, 1 H, NH), 4.52 (m, 1 H, α-hydrogen), 4.10 (m, 1 H, α-hydrogen), 3.70 (s superimposed on m, 4 H, *O*-methyl and cyclohexyl H_4), 2.3–1.0 (m, valyl methine and cyclohexyl excluding H_4), 1.42 (s, *tert*-butyl), 1.32 (d, alanyl methyl), 0.91 (q, valyl isopropyl), integration for last four peaks totals 28 hydrogens.

Anal. Calcd for $C_{21}H_{37}N_3O_6$: C, 59.0, H, 8.72; N, 9.83. Found: C, 58.8; H, 9.06; N, 9.62.

***N-tert*-Butyloxycarbonyl-L-alanine-*cis*-4-aminocyclohexanecarbonyl-L-valine Methyl Ester (6b).** *N-tert*-Butyloxycarbonyl-*cis*-4-aminocyclohexanecarbonyl-L-valine methyl ester (0.71 g, 2.0 mmol) was dissolved in 3 ml of trifluoroacetic acid and allowed to stand overnight. The solvent was removed *in vacuo*, the residue was dissolved in 10 ml of dimethylformamide, and 0.21 g (2.1 mmol) of triethylamine and 0.38 g (2.0 mmol) of *N-tert*-butyloxycarbonyl-L-alanine were added. The solution was cooled to 0° and 0.33 g (2.0 mmol) of diethylphosphoryl cyanide and 0.21 g (2.1 mmol) of triethylamine were added. The reaction mixture was stirred at 0° for 1 hr and at room temperature overnight. The mixture was diluted with water and extracted with ethyl acetate (3 × 10 ml). The ethyl acetate extracts were washed with 10% sodium bicarbonate, water, and 10% citric acid. The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 0.40 g of an oil (47%). This oil was crystallized from ethyl acetate–cyclohexane to give white crystals: mp 146–148°; R_f 0.78; $[\alpha]^{21}D$ − 12.6° (*c* 2.0, DMF); nmr ($CDCl_3$) δ 6.4 (d, 1 H, NH), 6.1 (d, 1 H, NH), 4.9 (d, 1H, NH), 4.7–3.8 (m, 3 H, α-hydrogens, cyclohexyl H_4), 3.70 (s, 3 H, methyl ester), 2.5–1.9 (m, 2 H, valyl methine, cyclohexyl H_1), 1.7 (br s, 8 H, cyclohexyl excluding H_1 and H_4), 1.45 (s, 9 H, *tert*-butyl), 1.35 (d, 3 H, alanyl methyl), 0.90 (q, 6 H, valyl isopropyl).

Anal. Calcd for $C_{21}H_{37}N_3O_6$: C, 59.0; H, 8.72; N, 9.83. Found: C, 59.3; H, 8.57; N, 9.60.

***p*-Nitrophenyl *N-tert*-Butyloxycarbonyl-*trans*-4-aminocyclohexanecarboxylate.** To a precooled solution of 0.96 g (3.95 mmol) of *N-tert*-butyloxycarbonyl-*trans*-4-aminocyclohexanecarboxylic acid and 2.20 g (15.8 mmol) of *p*-nitrophenyl in 5 ml of dimethylformamide was added 0.90 g (4.35 mmol) of *N,N'*-dicyclohexylcarbodiimide. The reaction mixture was stirred overnight at room temperature following which the dicyclohexyl urea was removed by filtration and the filtrate was evaporated *in vacuo* at 40°. The residue was crystallized from ethanol to give 0.67 g of white crystals (62%): mp 156–158°; R_f 0.76; nmr ($CDCl_3$) δ 1.8 (q, 4 H, nitrophenyl), 4.5 (d, 1 H, NH), 3.4 (s, 1 H, cyclohexyl H_4), 2.7–1.4 (m, 18 H, cyclohexyl except H_4, *tert*-butyl).

Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.3; H, 6.63; N, 7.76. Found: C, 59.2; H, 6.68; N, 7.48.

***p*-Nitrophenyl *N-tert*-Butyloxycarbonyl-*cis*-4-aminocyclohexanecarboxylate.** To an ice-cold solution of 0.97 g (4.07 mmol) of *N-tert*-butyloxycarbonyl-*cis*-4-aminocyclohexanecarboxylic acid and 2.28 g (16.4 mmol) of *p*-nitrophenol in 40 ml of ethyl acetate was added 0.92 g (4.5 mmol) of *N,N'*-dicyclohexylcarbodiimide and the reaction mixture was stirred overnight at 0°. *N,N'*-Dicyclohexylurea was removed by filtration and the filtrate was evaporated *in vacuo* to give an oil that slowly crystallized. Recrystallization from anhydrous ethanol gave 1.71 g (80%) of product: mp 132–134°; R_f 0.74; nmr ($CDCl_3$) δ 1.8 (q, 4 H, nitrophenyl), 3.6 (br s, 1 H, cyclohexyl H_4), 2.7 (br s, 1 H, cyclohexyl H_1), 2.4–1.6 (m, 8 H, cyclohexyl), 1.45 (s, 9 H, *tert*-butyl).

Preparation of *N-tert*-Butyloxycarbonyl-*cis*-4-aminocyclohexanecarbonylglycine Ethyl Ester (5) by the Active Ester Method. To a solution of 0.73 g (2 mmol) of *p*-nitrophenyl *N-tert*-butyloxycarbonyl-*cis*-4-aminocyclohexanecarboxylate and 0.28 g (2 mmol) of glycine ethyl ester hydrochloride in 5 ml of DMF was added 0.21 g (2 mmol) of triethylamine. After stirring overnight, tlc analysis of the reaction mixture indicated little reaction to have occurred. Imidazole (2.0 g) was added and the reaction mixture was stirred for 7 hr at which time tlc analysis showed the reaction to be complete. The reaction mixture was diluted with ethyl acetate and the organic phase was washed with 10% $NaHCO_3$, 10% citric acid, and water. The organic phase was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give 0.23 g of an oil. The residue was recrystallized from ether–petroleum ether (bp 60–90°) to yield 0.13 g (20%) of **5**, mp 125–128°. Tlc comparison of this material with a sample of **5** prepared above showed identical R_f values.

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Registry No.—**2a,** 3685-25-4; **2b,** 3685-23-2; **3a,** 53292-89-0; **3b,** 53292-90-3; **4a,** 53292-91-4; **4b,** 53368-40-4; **5,** 53292-92-5; **6a,** 53292-93-6; **6b,** 53368-41-5; *tert*-butyloxycarbonyl azide, 1070-19-5; L-valine methyl ester hydrochloride, 6306-52-1; pivaloyl chloride, 3282-30-2; glycine ethyl ester hydrochloride, 623-33-6; *N-tert*-butyloxycarbonyl-L-alinine, 15761-38-3; *p*-nitrophenyl *N-tert*-butyloxycarbonyl-*trans*-4-aminocyclohexanecarboxylate, 53292-94-7; *p*-nitrophenol, 100-02-7; *p*-nitrophenyl *N-tert*-butyloxycarbonyl-*cis*-4-aminocyclohexenecarboxylate, 53292-95-8.

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(11) See ref 3d for a case of formation of the symmetrical anhydride from a cyclohexaneamino acid derivative.

Pyrimidine Derivatives and Related Compounds. XXV.[1] The Synthesis of 6-Cyanouracil Derivatives and the Conversion of 6-Cyano-1,3-dimethyluracil to 5-Cyano Compound[2]

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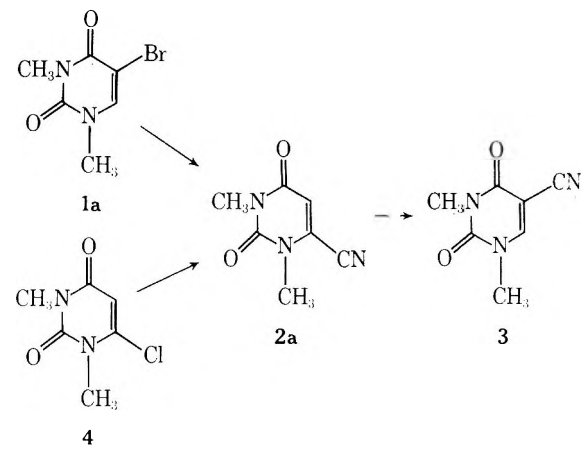
5-Bromo-1,3-dimethyluracil (**1a**) reacted with equimolar sodium cyanide in dimethylformamide (DMF) to give 6-cyano-1,3-dimethyluracil (**2a**), which was also obtained from 6-chloro-1,3-dimethyluracil (**4**) by the same treatment as above. Compound **2a** was readily converted to 5-cyano-1,3-dimethyluracil (**3**) when heated with a catalytic amount of sodium cyanide in DMF. The mechanism for these cine substitutions was shown by deuterium-exchange experiments to involve an addition–elimination process. Furthermore, a variety of N-substituted 6-cyanouracils (**2b,c** and **14a,c**) and N-substituted 6-carbamoyluracils (**12a–c**) were prepared by the reaction of 5-bromouracils (**1a–c** and **13a,c**) with sodium cyanide in DMF or 50% aqueous ethanol.

The chemistry of 5-substituted uracils[3] bearing an electron-withdrawing group at the 5 position, *e.g.*, 5-nitro-,[4] 5-formyl-,[5] and 5-carboxyuracils,[6] has been already studied by many investigators. We previously reported the synthesis of 5-cyanouracil derivatives[7] and the hydrolysis[8] and reduction[9] of their cyano group. Meanwhile, 6-cyanouracil derivatives are very interesting in potential biological activity as orotic analogs. However, synthesis of such 6-cyanouracils has not been widely done yet. Only Ueda, *et al.*,[10] reported the formation of the 6-cyanouridine derivative together with the 5-cyano relative by treatment of the 5-bromouridine derivative with 5 equiv of sodium cyanide. In this paper, we report that treatment of 5-bromouracils and 6-cyanouracils with sodium cyanide causes cine substitution to give 6-cyanouracils and 5-cyanouracils, respectively.

5-Bromo-1,3-dimethyluracil (**1a**) was selected as a model compound for examining of the mode of reaction of 5-bromouracil derivatives with sodium cyanide. At first, **1a** was treated with a large excess of sodium cyanide in dimethylformamide (DMF) at 80° for 2 hr to afford the known[11] 5-cyano-1,3-dimethyluracil (**3**) in 68% yield. When **1a** was, however, allowed to react with an equimolar sodium cyanide in DMF at room temperature for 2 hr, the sole product which we could isolate in high yield was not **3**, but 6-cyano-1,3-dimethyluracil (**2a**). The structure of **2a** was fully supported by its spectral and elemental analyses. The proton magnetic resonance (pmr) spectrum of this compound in deuteriochloroform ($CDCl_3$) showed a sharp singlet (1 H) at δ 6.30, corresponding to the absorption for the C-5 proton (δ 5.73) of 1,3-dimethyluracil but did not show an absorption for the C-6 proton (δ 7.98) as observed in **3**. The infrared (ir) spectrum indicated a weak CN peak at 2240 cm^{-1}, unlike a strong CN peak of **3** at 2220 cm^{-1}. The optimum condition for the synthesis of **2a** from **1a** was the use of equimolar sodium cyanide with **1a** at room temperature in DMF as a solvent.

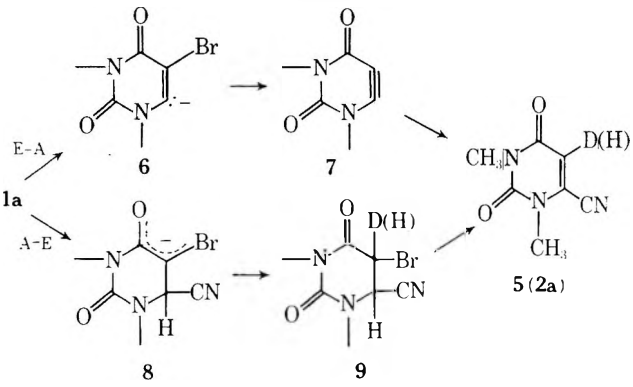
By the way, Liebenow, *et al.*,[12] obtained **3** in 73% yield by treating 6-chloro-1,3-dimethyluracil (**4**) with excess potassium cyanide in dimethyl sulfoxide (DMSO) at 90–110°. In our laboratory, however, compound **4** gave **2a** in high yield when the reaction was carried out with equimolar sodium cyanide in dry DMF at room temperature for 2 hr. Although **2a** was not converted to **3** in the absence of sodium cyanide, the desired **3** was obtained by treating **2a** in DMF at 80° with a catalytic amount of sodium cyanide. On the contrary, the conversion of **3** to **2a** was unsuccessful under the same conditions as above. Furthermore, it was found that occurrence of the reaction was greatly dependent on the reaction medium; in an aprotic polar solvent such as DMF and DMSO, the conversion proceeded, but in a protic polar solvent such as water and ethanol, alternative reactions occurred to give 6-carbamoyl-1,3-dimethyluracil (**12a**) and ethyl imidate (**15a**),[13] respectively. From these results, it appeared that the reaction of **1a** and **4** with sodium cyanide proceeds by the following steps: (**1a** and **4**) → **2a** → **3a** (Scheme I).

Scheme I

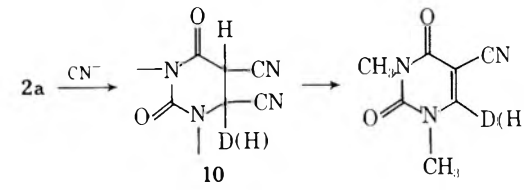


Because of the low reactivity of the 5-bromine atom, 5-bromouracils undergo substitution with amines[14] or base-catalyzed hydrolysis[15] under drastic conditions only. However, recent studies have revealed that 5-bromouracils can be easily debrominated with sulfur-containing reagents such as NaSH,[16] Na_2SO_3,[17] $NaHSO_3$,[18] and cysteine.[19] The mechanism of the above reaction most likely involves an addition–elimination mechanism, initiated by nucleophilic attack of an anion at the C-6 position, followed by formation of the 5,6-dihydrouracil intermediate, and then removal of the bromine.[16,19a] In this connection, two possible mechanisms for the cine substitution of **1a** to **2a** are suggested:[20,21] one is an addition–elimination (A–E) mechanism, as described above, and another is an elimination–addition (E–A) mechanism *via* deprotonation at the C-6 proton of the uracil ring and formation of a hetaryne. Hetaryne formation has been well investigated in halogenoheterocyclic aromatic compounds by Kauffmann[21] and van der Plas.[22] In order to elucidate the mechanism, **1a** was treated with sodium cyanide using DMF–D_2O (10 equiv of D_2O to **1a**) as a solvent. Although an intermediate addition product could not be detected, the final product was 6-

Scheme II



Scheme III

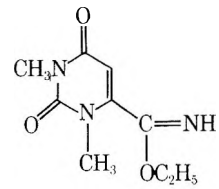


cyano-5-deuterio-1,3-dimethyluracil (**5**) in which 85% of the hydrogen was exchanged with deuterium at the C-5 position, as indicated by integration of its diminished C-5 hydrogen peak in the pmr spectrum. The participation of D_2O in this reaction reasonably supports the A–E mechanism rather than the E–A mechanism. That is, if the E–A mechanism were involved, the addition of D_2O (H_2O), a good protonating agent for the carbanion precursor **6** of pyrimidyne (**7**), would inhibit the reaction.[23] Actually D_2O had no influence on the reaction and a deuterium atom was incorporated into the C-5 position. Thus, the mechanism would be as follows: the initial nucleophilic attack by cyanide occurs at C-6 to give a carbanion **8**, which forms the 5,6-dihydro intermediate **9** by abstraction of a deuterium (proton) from D_2O (H_2O), and, at last, dehydrobromination of **9** gives **5** (**2a**) (Scheme II).

The mechanism for conversion of **2a** to **3** was then studied. Thus **2a** was allowed to react with a catalytic amount of sodium cyanide in the presence of 10 equiv of D_2O to yield 5-cyano-6-deuterio-1,3-dimethyluracil (**11**), in which 84% of C-6 hydrogen was exchanged with deuterium. D_2O (H_2O) was also concerned in this conversion as well as in the reaction of **1a** to **2a**. In view of the above, we presumed that the most likely mechanism for this reaction might involve a 1,2 addition, initiated by a nucleophilic attack of cyanide at C-5, followed by abstraction of a deuterium (proton) from D_2O (H_2O) at C-6. Then, hydrogen cyanide would be removed from the resulting 5,6-dihydrouracil intermediate **10** to give **11** (**3**) (Scheme III).

Fox, *et al.*, once proposed[24] such a mechanism involving an initial "C-5 attack" to account for the exchange of H-6 for deuterium in 5-halogenouracils, but they have withdrawn it recently.[25] The present case involving "C-5 attack" is therefore the first example of an A–E mechanism and is rather unusual in uracil derivatives compared with that caused by "C-6 attack."

We have investigated the reaction of N-substituted 5-bromouracil derivatives with sodium cyanide in more detail and the results are summarized in Table I. The reactions are classified into three types according to the presence or absence of a substituent at N-1 or/and N-3. In the case of type I, 1,3-disubstituted 5-bromouracils **1**, alkylated in both 1 and 3 positions, gave good yields of 1,3-disubstituted 6-cyanouracils **2** when allowed to react with equimolar sodium cyanide in DMF at room temperature (method A). When the reaction was carried out in refluxing 50% ethanol instead of DMF, 1,3-disubstituted 6-carbamoyluracils **12**, where the cyano group was further hydrolyzed, were obtained (method B). It is reasonable to assume that the reaction proceeds by way of **2** and an imidate **15**, because of the fact that **2a** readily formed an imidate **15a** when **1a** in ethanol solution was subjected to the action of a catalytic amount of an alkali; the resulting **15a** underwent base-catalyzed hydrolysis to afford **12a**. 1-Substituted 5-bromouracils **13** having no substituent at the N-3 position were then subjected to the reactions of methods A and B to give 1-substituted 6-cyanouracils **14** only (type II). Compound **14** failed to give an imidate under the same conditions as described in the formation of **15a**, and this would be the reason why **14** was no longer hydrolyzed to 6-carbamoyl compounds. As to 3-substituted 5-bromouracils (example, 3-substituent; H, CH_3, and C_4H_9) which are not alkylated at N-1, the desired 6-cyano compound was not obtained but only salt formation between these acidic N(1)-H and sodium cyanide was observed (type III).



15a

As described above, the reaction between N-substituted 5-bromouracils and sodium cyanide is greatly influenced by the presence of substituents at N-1 and N-3; properties of substituents such as steric hindrance and electron attractivity have no marked influence on the reaction.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and were uncorrected. Pmr spectra were determined on a 60-Mc Hitachi Perkin-Elmer R-20B spectrometer using $CDCl_3$ as a solvent and tetramethylsilane as an internal reference. Ir spectra were obtained with a Hitachi 215 instrument as KBr pellets.

Formation of 6-Cyano- (or Carbamoyl-) uracils. General Procedure. Method A. To a stirred suspension of the 5-bromouracil derivative (0.005 mol) in 10–15 ml of DMF was added a solution of NaCN (0.29 g, 0.006 mol) in 0.5 ml of water and the mixture was stirred at room temperature . After the reaction was complete, the mixture was poured into *ca.* 100 ml of chilled water. Depending on the solubility of the product in the solvent, the 6-cyano compound was either isolated by filtration or extracted with $CHCl_3$, dried, and evaporated *in vacuo*. The resulting crude product was recrystallized (see Table I).

Method B. A mixture of the 5-bromouracil derivative (0.005 mol) and NaCN (0.29 g, 0.006 mol) was refluxed in 20 ml of 50% aqueous ethanol. After the reactants were dissolved, refluxing was continued for a further 1–2 hr. The solution was evaporated to dryness *in vacuo* and the residue was triturated with 50 ml of cold water and acidified with HCl. The precipitate was collected by filtration and recrystallized (see Table I).

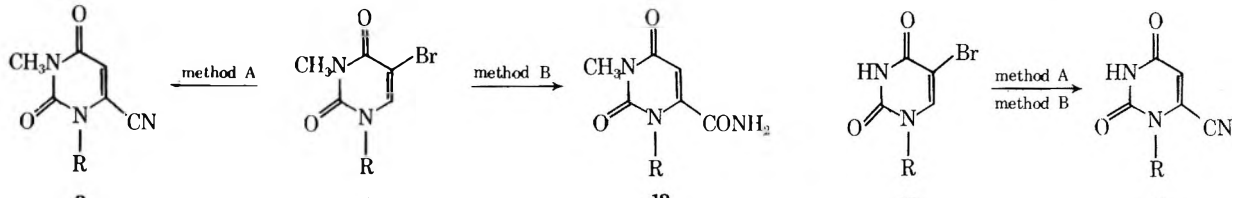
5-Cyano-1,3-dimethyluracil (3). (a) A mixture of 1.1 g (0.005 mol) of 5-bromo-1,3-dimethyluracil (**1a**) and 0.58 g (0.012 mol) of NaCN in 1 ml of DMF was heated at 80–90° for 2 hr. The solvent was evaporated *in vacuo*. To the residue was added 5 ml of water and the precipitate was collected by filtration, giving 0.76 g (92%) of the crude product, mp 162–164°. Recrystallization from ethanol afforded colorless needles: mp 165° (lit.[11] mp 165°); ir ν max 2220 (CN), 1720, and 1650 cm^{-1} (C=O); pmr ($CDCl_3$) δ 3.54 (3 H, s, NCH_3), 3.40 (3 H, s, NCH_3), and 7.98 ppm (1 H, s, 6-CH).

Anal. Calcd for $C_7H_7O_2N_3$: C 50.91; H, 4.27; N. 25.45. Found: C, 50.93; H, 4.28; N, 25.54.

Table I

Formation of N-Substituted 6-Cyano- (or Carbamoyl-) uracils from 5-Bromouracils with Sodium Cyanide

Type I Type II



2 1 12 13 14

Starting material	R	Method[a]	Time, hr	Product	Yield, %	Mp, °C (solvent) of recrystn	Spectral data: Pmr,[b] δ, ppm (5-CH)	Spectral data: Ir, cm⁻¹ (C≡N)	Formula	Calcd (found) C	H	N
1a	CH_3	A	2	**2a**	95	168–170 (EtOH)	6.34	2240	$C_7H_7O_2N_3$	50.91 (51.05)	4.27 4.30	25.45 25.72)
1a	CH_3	B	2	**12a**[c]	86	238–239 (MeOH)[d]	5.81		$C_7H_9O_3N_3$	45.90 (46.10)	4.95 5.14	22.94 22.76)
1b	C_6H_{11}	A	24	**2b**	94	209–211 (EtOH)	6.27	2235	$C_{12}H_{15}O_2N_3$	61.78 (61.49)	6.48 6.44	18.02 17.50)
1b	C_6H_{11}	B	3	**12b**	93	179–180 (H_2O)	5.65		$C_{12}H_{17}O_3N_3$	57.35 (57.29)	6.81 6.84	16.72 16.90)
1c	C_6H_5	A	1	**2c**	86	205 (EtOH)	6.38	2250	$C_{12}H_9O_2N_3$	63.43 (63.25)	3.99 4.11	18.49 18.39)
1c	C_6H_5	B	2	**12c**	90	274–275 (MeOH)	5.92		$C_{12}H_{11}O_3N_3$	58.77 (58.98)	4.52 4.56	17.14 16.83)
13a	CH_3	A	5	**14a**	53	228–229 (H_2O)	6.36	2240	$C_6H_5O_2N_3$	47.68 (47.54)	3.34 3.32	27.81 27.94)
		B	2		93							
13c	C_6H_5	A	6	**14c**	69	242–245 (EtOH)	6.42	2250	$C_{11}H_7O_2N_3$	61.97 (61.90)	3.31 3.32	19.71 19.58)

[a] See Experimental Section. [b] Solvents: **2a–c**, $CDCl_3$; **12a–c** and **14a, c**, DMSO-d_6. [c] Alternate synthesis reported: K. A. Chkhivadze, N. E. Britikova, and O. Y. Magidson, *Biol. Akt. Soedin.*, 22 (1965) [*Chem. Abstr.*, **63**,18081*a* (1960)]. [d] Lit. mp 239° (H_2O).

(**b**) To a solution of 0.83 g (0.005 mol) of 6-cyano-1,3-dimethyluracil (**2a**) in 5 ml of DMF was added 30 mg (0.6 mmol) of NaCN. The mixture was heated at 80–85° for 5 hr and the solvent was removed by evaporation. To the residue was added 50 ml of cold water and the precipitate was filtered, washed with water, and recrystallized from ethanol to give 0.5 g (67.5%) of colorless needles of **3**.

6-Cyano-1,3-dimethyluracil (2a) from 6-Chloro-1,3-dimethyluracil (4). To a stirred solution of 0.87 g (0.005 mol) of **4** in 10 ml of DMF[26] was added 0.29 g (0.006 mol) of NaCN. The reaction mixture was maintained at room temperature for 2 hr and poured into *ca.* 100 ml of ice–water. The precipitate was filtered, washed with cold water, and recrystallized to give 0.7 g (88%) of the product **2a**, which was identified by ir and pmr spectra and mixture melting point with an authentic sample prepared from 5-bromo-1,3-dimethyluracil.

6-Cyano-5-deuterio-1,3-dimethyluracil (5). To a solution of 1.1 g (0.005 mol) of 5-bromo-1,3-dimethyluracil (**1a**) in 15 ml of DMF[26] was added 0.9 ml (0.5 mol) of D_2O and 0.29 g (0.006 mol) of NaCN with stirring at room temperature. The reaction mixture was treated as described above for the preparation of **2a** to give 0.83 g of **5**; the pmr spectrum ($CDCl_3$) showed that 85% of H-5 exchanged with deuterium; the remainder of the spectrum was identical with that of **2a**; ir ν max 2290 cm^{-1} (C–D).

5-Cyano-6-deuterio-1,3-dimethyluracil (11). To a solution of 0.83 g (0.005 mol) of 6-cyano-1,3-dimethyluracil (**2a**) in 10 ml of DMF[26] were added 0.9 ml (0.05 mol) of D_2O and 30 mg (0.0006 mol) of NaCN. Work-up of the reaction product was the same as in the reaction of **2a** to **3**, to give 0.80 g of **11**; pmr ($CDCl_3$) showed that 84% of H-6 exchanged with deuterium; the remainder of the spectrum was identical with that of **3**; ir ν max 2290 cm^{-1} (C–D).

Ethyl 6-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro)pyrimidylimidate (15a). (**a**) A mixture of 0.83 g (0.005 mol) of **2a** and 0.028 g (0.0005 mol) of potassium hydroxide in 10 ml of ethanol was refluxed for 1 hr. After neutralization with hydrochloric acid, the solution was evaporated *in vacuo* and the residue was triturated with 1 ml of cold water. Filtration then gave 0.90 g (85%) of **15a**. An analytical sample was recrystallized from ligroine: mp 98–100°; ir ν max 3330 cm^{-1} (NH); pmr ($CDCl_3$) δ 1.39 (3 H, t, J = 8 Hz, CH_2CH_3), 3.38 (6 H, s, $2NCH_3$), 4.35 (2 H, q, J = 8 Hz, OCH_2), and 5.81 ppm (1 H, s, 5-CH).

Anal. Calcd for $C_9H_{13}O_3N_3$: C, 51.17; H, 6.20; N, 19.90. Found: C, 50.89; H, 6.00; N, 20.06.

(**b**) Compound **2a** was treated with 0.1 equiv of sodium cyanide instead of potassium hydroxide by the same procedure as described above to give **15a** in 63% yield, identical with a sample prepared in method a.

6-Carbamoyl-1,3-dimethyluracil (12a). (**a**) A suspension of 0.49 g (0.0025 mol) of **15a** in 5 ml of a 5% aqueous solution of sodium hydroxide was refluxed for 10 min. The soluton was neutralized with hydrochloric acid and concentrated *in vacuo*. The residual solid was washed with cold water to give 0.48 g (52%) of the crude product. Recrystallization from methanol gave the colorless needles of **12a**.

(**b**) A mixture of 0.83 g (0.005 mol) of **2a** and 0.025 g (0.0005 mol) of sodium cyanide in 10 ml of water was refluxed for 1 hr. After neutralization with hydrochloric acid, the solution was evaporated *in vacuo* and the residue was triturated with cold water. Filtration then gave the crude product of **12a** in 71% yield, identical with a sample prepared in method a.

Registry No.—**1a**, 7033-39-8; **1b**, 53293-08-6; **1c**, 53369-64-5; **2a**, 49846-86-8; **2b**, 53293-09-7; **2c**, 53293-10-0; **3**, 36980-91-3; **4**, 6972-27-6; **5**, 53293-11-1; **11**, 53293-12-2; **12a**, 2019-20-7; **12b**, 53293-13-3; **12c**, 53369-65-6; **13a**, 6327-97-5; **13c**, 53369-66-7; **14a**, 53293-14-4; **14c**, 53293-15-5; **15a**, 53293-16-6; NaCN, 143-33-9.

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Linear Benzoadenine. A Stretched-Out Analog of Adenine

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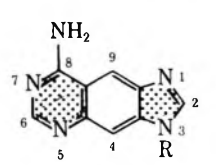
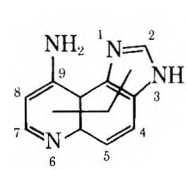
The synthesis of 8-aminoimidazo[4,5-*g*]quinazoline (**1**), an extended or "stretched-out" version of adenine which is given the descriptive name *lin*-benzoadenine, is reported. The synthesis involves the elaboration of 7-chloro-4-quinazolone (**6**) to imidazo[4,5-*g*]quinazolin-8-one (**11**) in four steps, followed by thiation to 8-mercaptoimidazo[4,5-*g*]quinazoline (**12**) and subsequent replacement of the thiol function by ammonia to yield the *lin*-benzoadenine isomer **1**. The aralkyl derivatives of **1**, *e.g.*, 8-amino-1- and 3-benzylimidazo[4,5-*g*]quinazoline (**17** and **16**), which are necessary to serve as uv models in assigning the structure of nucleoside and nucleotide targets and to direct further substitution, were obtained indirectly *via* benzylation of 8-methylthioimidazo[4,5-*g*]quinazoline (**13**). The structure assignment of the 3-benzyl isomer was checked by an unambiguous synthesis, and its value as a uv model was confirmed by spectral comparison with 8-amino-3-cyclohexylaminoimidazo[4,5-*g*]quinazoline (**30**). A general comparison of the uv spectra of various 8-methylthio- and 8-aminoimidazo[4,5-*g*]quinazoline derivatives in neutral, acidic, and basic solution indicates that first protonation occurs mainly on the imidazole ring of the methylthio compounds and on the quinazoline ring of the amino compounds.

There has been considerable interest in the synthesis of analogs of the naturally occurring nucleic acid bases and their corresponding nucleosides, nucleotides, and coenzymes.[1] In the course of our continuing study of the role of purines and pyrimidines in nature, we questioned what properties might be associated with compounds in which the pyrimidine ring and the imidazole ring of the purine system are separated by a benzene ring to form an extended or "stretched-out" purine model. Compounds such as **1** and **1a** would be expected to have 1,N^6 binding sites similar to those in adenine and adenosine, stronger π-bonding characteristics, and larger spatial requirements. The physical and biological properties of compounds **1** and **1a** and their congeners hold considerable interest since they are previously unknown and since differences in their behavior in relation to the corresponding naturally occurring adenine compounds might be relatable to defined geometrical changes.

In this paper we describe the synthesis, structure proof, and properties of the linear benzolog of adenine, 8-aminoimidazo[4,5-*g*]quinazoline (**1**), for which we suggest the descriptive name *lin*-benzoadenine.[2] This name is capable of easy adaptation to derivatives related to adenosine, adenylic acid, adenosine 5′-diphosphate, and the like. In the following paper we discuss the preparation of the structural isomers of **1**, 9-aminoimidazo[4,5-*f*]quinazoline (**2**) and 6-aminoimidazo[4,5-*h*]quinazoline (**3**), which are the proximal and distal isomers of benzoadenine, respectively.[2] We feel justified in using the term "benzo" in the trivial names of these three compounds because *only when the additional ring is central* does it contain no nitrogens and is accordingly "benzo."



1, R = H
1a, R = β-D-ribofuranosyl



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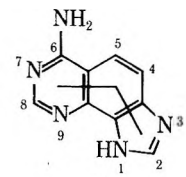
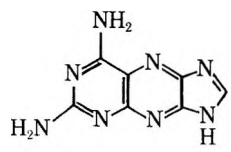


3

A review of the literature reveals only several cases where tricyclic heterocyclic systems related to **1** have been described. For none of the compounds was their preparation based on the criterion that they might be biologically active as purine surrogates. Taylor and Sherman synthesized diamino compound **4** during the course of work on



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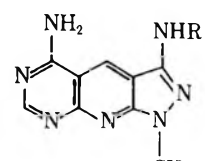
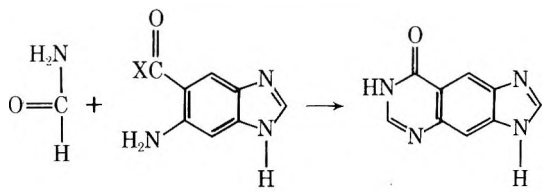


5, R = H, CHO, $COCH_3$

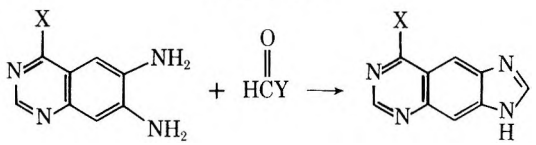
pteridine compounds.[3] Derivatives of **5** were synthesized and discussed on the basis of their relationship to tetrasubstituted pyridines.[4]

We approached the synthesis of the *lin*-benzoadenine **1** with the view that its preparation should be relatively simple and amenable to large batch scale-up. At first inspection, three possible routes to this ring system seem viable: the fusion of a pyrimidine ring onto an appropriately substituted benzimidazole (Scheme I); the construction of an imidazole moiety onto a disubstituted quinazoline (Scheme II); or the annelation of a tetrasubstituted benzene ring to form both heterocyclic rings simultaneously (Scheme III).

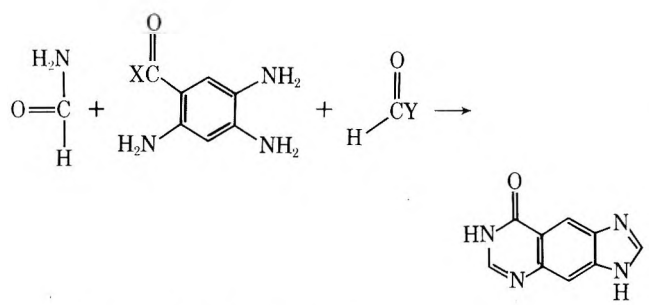
Scheme I



Scheme II



Scheme III



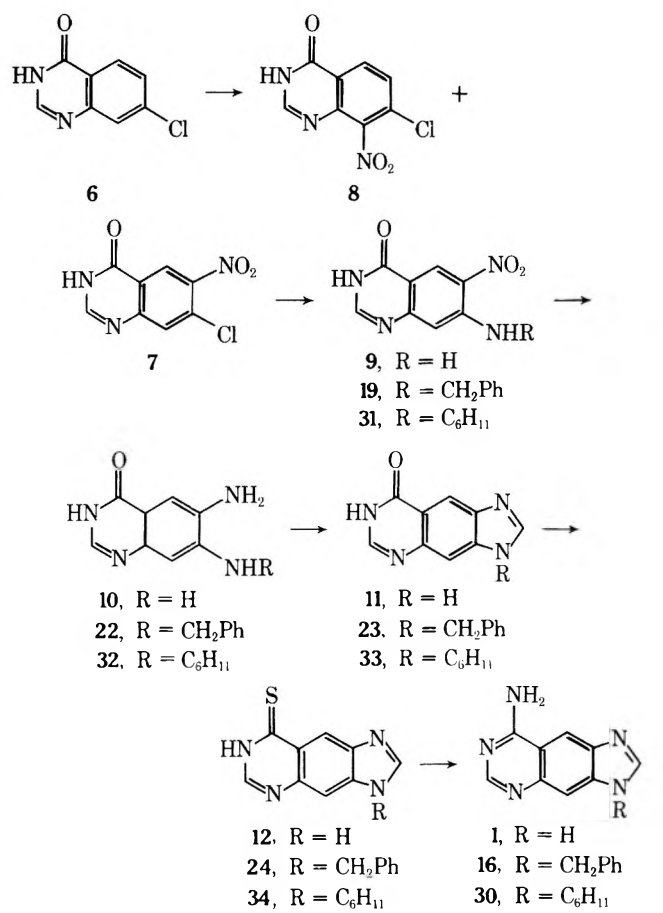
The first and third schemes were limited by the necessity for adjacent placement of aldehyde or ester and nitro or amino functions, which offered some synthetic difficulties. The polyfunctional substitution pattern required by Scheme III is probably synthetically accessible, although further elaboration of such a highly substituted benzene system might be limited because of the high reactivity inherent in such a system. The second scheme seemed most practical since the construction of monosubstituted quinazolones is well represented in the literature.[5] Further elaboration to a 6,7-disubstituted quinazoline as required by Scheme II appeared quite feasible and this, therefore, was the approach that we used.

Results and Discussion

Nitration of 7-chloro-4-quinazolone (**6**)[6] gave a 4:1 mixture (nmr) of the isomeric chloronitroquinazolones **7** and **8**, respectively. These isomers were separated by fractional crystallization, and the 6,7-disubstituted isomer **7** was obtained in 58% yield. The structure assigned to **7** was supported by the nmr spectrum which showed three singlet aromatic proton resonances at δ 7.97, 8.28, and 8.53. The nmr spectrum of the 7,8-disubstituted derivative **8** showed a singlet at δ 8.22 (H-2) and an AB quartet at δ 7.75 and 8.25 (H-5 and H-6). Treatment of compound **7** with butanolic ammonia in a sealed tube at 175° afforded 7-amino-6-nitro-4-quinazolone (**9**) in 98% yield. Reduction to diaminoquinazolone **10** could be effected by either catalytic hydrogenation or treatment with Raney nickel and hydrazine hydrate.[7] Ring closure proceeded readily in formic acid to give imidazoquinazolone **11**. Treatment of **11** with phosphorus pentasulfide in pyridine afforded the corresponding thio compound **12**. Compound **12** was converted to *lin*-benzoadenine **1** (8-aminoimidazo[4,5-*g*]quinazoline) upon heating in ammonia-saturated butanol in a sealed tube at 200°.

This compound (**1**) proved to be extremely insoluble in water and nonacidic organic solvents such as chloroform, acetonitrile, dimethylformamide, and dimethyl sulfoxide. This insolubility imposed experimental problems in assessing the reactivity of the compound. In particular, compound **1** did not react with alkylating reagents such as benzyl bromide or methyl iodide under normal reaction conditions. This was especially inconvenient since it was necessary to determine the preferred sites of alkylation and to prepare alkyl derivatives of **1** which would serve as uv models to aid in the structure assignment of the nucleoside and nucleotide target compounds. Consequently, an indirect approach was undertaken. The alkylation of the very soluble methylthio analog (**13**) of **1** was investigated. Compound **13**, easily prepared by the S-methylation of **12**, was readily convertible to the linear benzoadenine upon treatment with butanolic ammonia. It was anticipated that the derivatives obtained from the alkylation of **13** could also be easily converted to their respective benzoadenine derivatives (Scheme IV).

Scheme IV



The reaction of the methylthio compound **13** with benzyl bromide and potassium carbonate in dimethylformamide at room temperature resulted in nearly equal amounts of two isomeric benzyl derivatives, **14** and **15**. Both isomers **14**

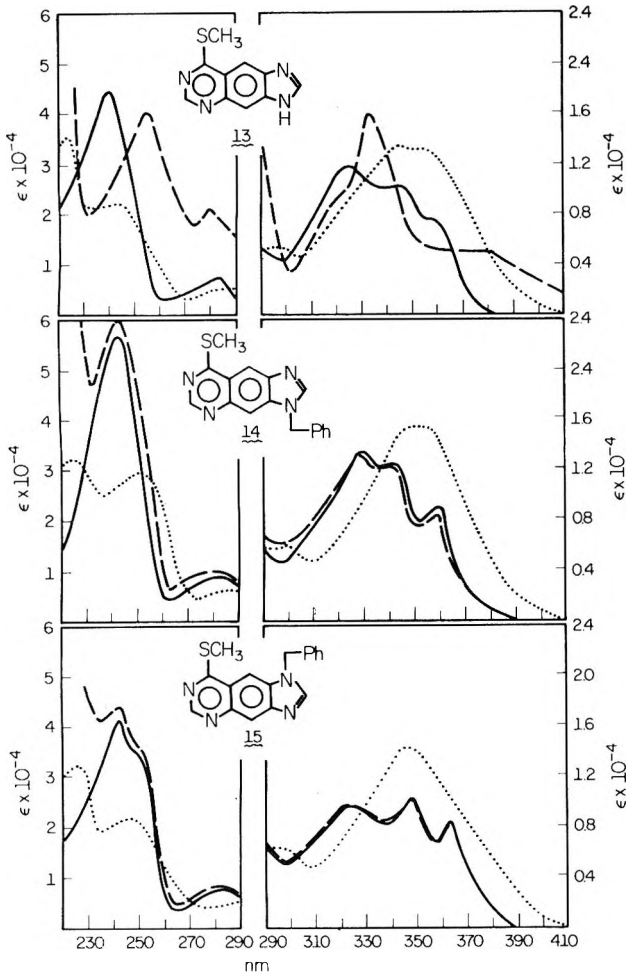


Figure 1. The uv spectra of 8-methylthioimidazo[4,5-*g*]quinazoline and its derivatives in 95% ethanol (——), 0.1 *N* HCl in 95% ethanol (· · · ·), and 0.1 *N* NaOH in 95% ethanol (- - - -).

and **15** could be converted to their respective amino analogs **16** and **17**, derivatives of *lin*-benzoadenine **1**. That the two pairs of benzyl derivatives (**14**, **15** and **16**, **17**) had similar spectral properties (as shown by a comparison of uv spectra in Figures 1 and 2) indicated that substitution had probably occurred at the anticipated positions, N-3 and N-1, of the methylthiobenzopurine **13**. In order to assign the structures of the benzylmethylthio derivatives as those indicated in **14** and **15**, 3-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (**14**) was prepared by an unambiguous synthesis.

Direct treatment of chloronitroquinazolone **7** with neat benzylamine interestingly afforded *N*-benzyl-2-amino-4-benzylamino-5-nitrobenzamide (**18**) as the sole isolable product. However, when the reaction was controlled using **7** with an excess of benzylamine in butanol as the solvent, the desired 7-benzylamino-6-nitro-4-quinazolone (**19**) was isolated. The ring opening of 4-quinazolones resulting from nucleophilic attack of neat primary amines to afford either anthranilamides or N-3 substituted quinazolones was reported some years ago from this laboratory.[8] In order to obtain further confirmation of the structures assigned to intermediates **18** and **19**, both compounds were converted to a dibenzylquinazolone **20** identical from both sources, from **18** by heating with formic acid and from **19** by reaction with potassium hydroxide and benzyl bromide in methanol. 3-Benzyl-7-benzylamino-6-nitro-4-quinazolone (**20**) was also prepared independently from **7** *via* benzylation to 3-benzyl-7-chloro-6-nitro-4-quinazolone (**21**) followed by benzylamine displacement in hot butanol. The quinazolone

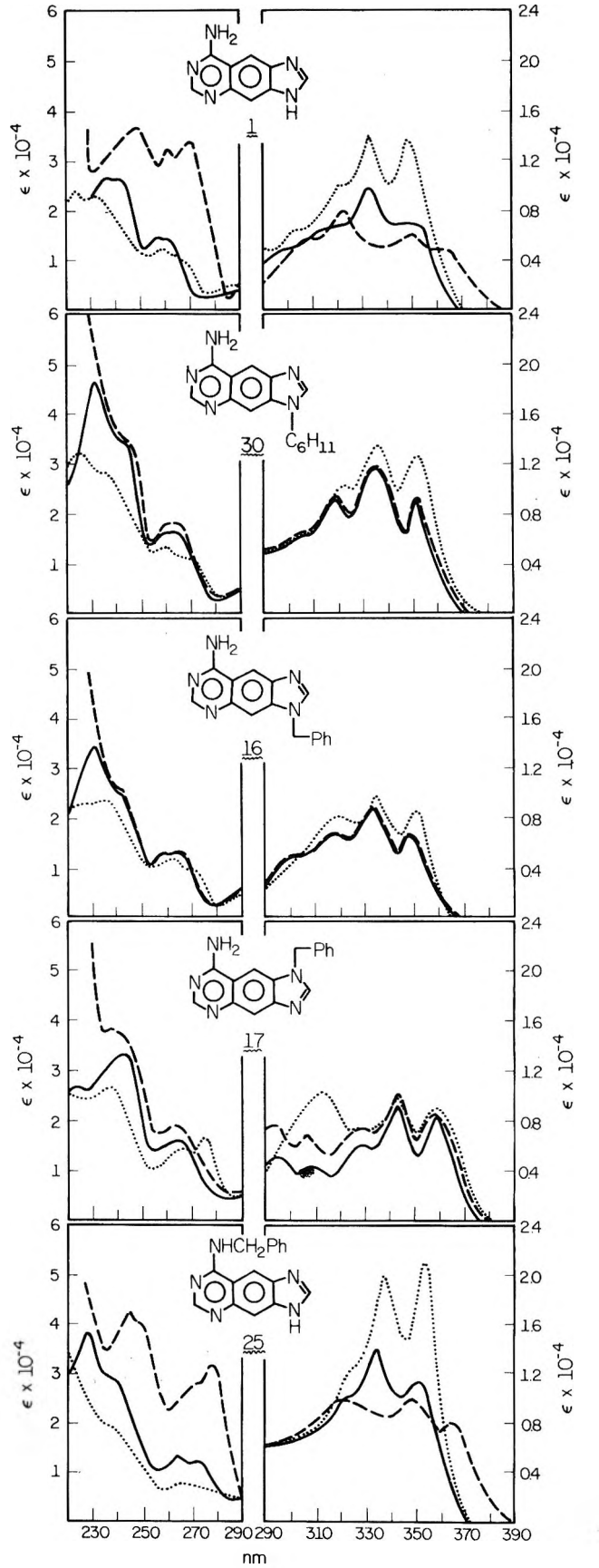
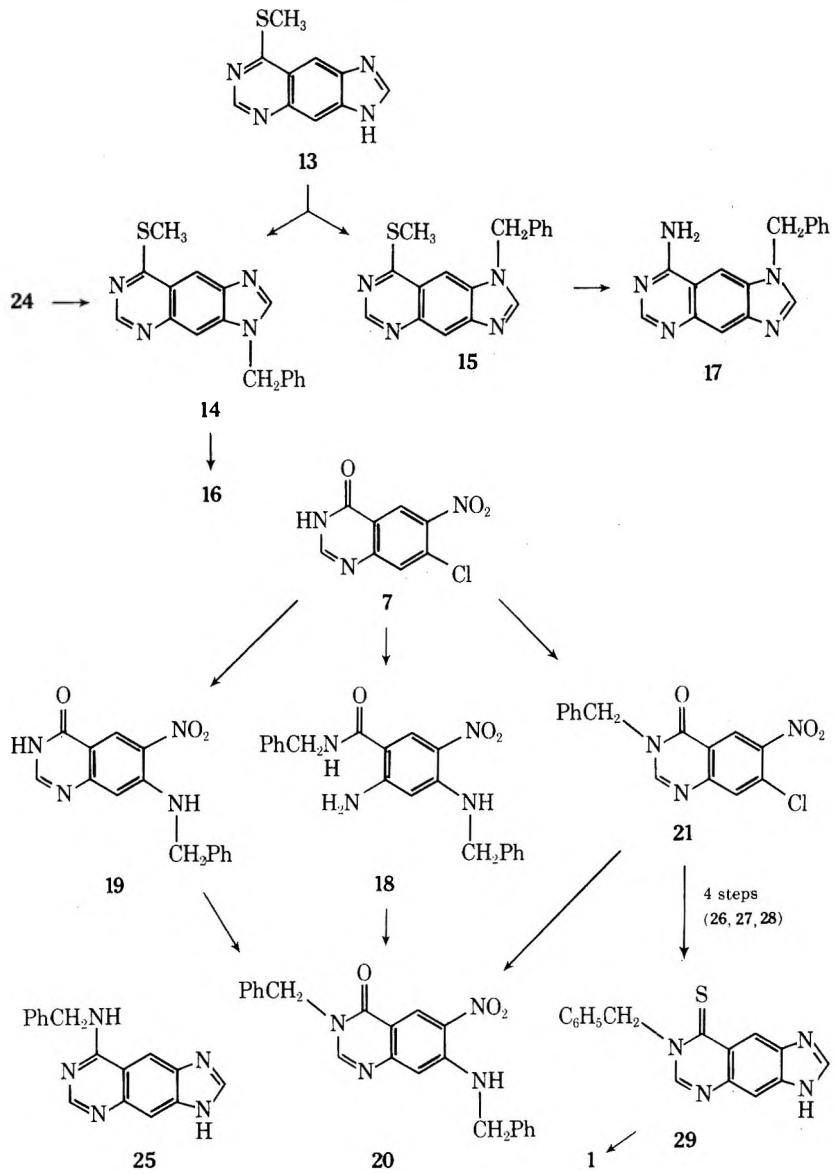


Figure 2. The uv spectra of *lin*-benzoadenine and its derivatives in 95% ethanol (——), 0.1 *N* HCl in 95% ethanol (· · · ·) (0.01 *N* HCl in 95% ethanol for **17**), and 0.1 *N* NaOH in 95% ethanol (- - - -).

19 was hydrogenated catalytically to the corresponding amino compound **22**. Cyclization in formic acid yielded 3-benzylimidazo[4,5-*g*]quinazolin-8-one (**23**), which was then

Scheme V



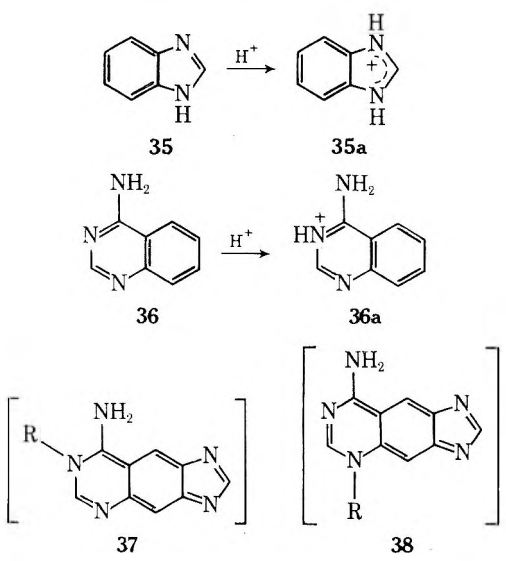
converted to the corresponding thio compound **24** with phosphorus pentasulfide and pyridine. Alkylation of the potassium salt of **24** completed the unambiguous route to compound **14**, identical in all its properties with one of the alkylation products of methylthioimidazoquinazoline **13**. Both compounds **14** and **24** were converted to 8-amino-3-benzylimidazo[4,5-*g*]quinazoline (**16**) upon heating in a sealed tube with alcoholic ammonia. This compound (**16**) was debenzylated with sodium in liquid ammonia to afford the unsubstituted compound **1** described above (Scheme V).

The preparation of other possible isomers of **16** and **17** was also investigated. Thus, 8-benzylaminoimidazo[4,5-*g*]quinazoline (**25**) was obtained from the reaction of the mercaptoquinazoline type **12** with benzylamine in ethanol. The preparation and isolation of isomers containing the benzyl substituent on either of the quinazoline nitrogens proved elusive, probably indicating the decreased stability of such compounds. Thus, when 3-benzyl-7-chloro-6-nitro-4-quinazolone (**21**) was treated with alcoholic ammonia, the corresponding nitroamine **26** was isolated, which was reduced to 3-benzyl-6,7-diamino-4-quinazolone (**27**), and this was condensed with formic acid to yield 7-benzylimidazo[4,5-*g*]quinazolin-8-one (**28**). Subsequent thiation afforded mercapto derivative **29**. Surprisingly, the reaction of **29** with alcoholic ammonia proceeded with the apparent loss of benzylamine to afford the unsubstituted *lin*-benzoadenine **1** directly.

The preparation of the stable benzyl derivatives of **1** was important both in determining the mode of alkylation and in providing uv models which would be necessary for assigning the structures of nucleoside derivatives of **1**. In this latter respect, there was concern that the chromophore inherent in the benzyl substituents might either mask or perturb the uv absorption characteristic for the tricyclic ring systems of the substituted benzoadenines. In order to verify the usefulness of the benzyl-*lin*-benzoadenines as applicable uv models, a corresponding aliphatic derivative, 8-amino-3-cyclohexylimidazo[4,5-*g*]quinazoline (**30**), was also made by a route modeled after the syntheses described above, namely, from the chloronitro compound **7**, by displacement with cyclohexylamine (→**31**), reduction (→**32**), condensation (→**33**), thiation (→**34**), and finally treatment with alcoholic ammonia. A comparison of the uv spectra of the 3-cyclohexyl derivative **30** and the 3-benzyl derivative **16** shows that the absorption maxima due to the three highest wavelength transitions coincide exactly (Figure 2). This supports the usefulness of the two benzyl derivatives

16 and 17 as applicable uv models and indicates further that, for N-substituted *lin*-benzoadenines, the spectra will be more susceptible to the position of substitution than to the type of substitution (*e.g.*, alkyl, aryl, ribosyl) on the particular nitrogen.

The uv spectra of the methylthio- and amino-substituted imidazo[4,5-*g*]quinazolines as presented in Figures 1 and 2 illuminate some interesting electronic features of these compounds. It is apparent that the low-energy transitions of the *lin*-benzoadenines (**1, 16, 17,** and **30**) show only negligible shifts in adsorption maxima in neutral or acidic solution. The unsubstituted compound **1** shows a bathochromic shift in the long wavelength band in basic solution due to deprotonation of the imidazole ring. In contrast, the three low-energy transitions of the methylthio derivatives **13–15,** which are similar in neutral and basic solution, collapse to a broad peak in acidic solution, with a hypsochromic shift of the lowest energy absorption maxima observed in neutral solution. It is interesting to note that the uv spectrum of benzimidazole (**35**) is essentially unchanged in neutral or basic solution. In acidic solution, however, a marked hypsochromic shift of the low-energy band is observed, which is attributable to protonation on the imidazole ring (**35a**).[9] In contrast, 4-aminoquinazoline (**36**) exhibits nearly identical spectra in acidic, basic, and neutral solution.[10] This has been interpreted to represent protonation of the quinazoline ring, preferably at the N-3 position (**36a**).[10b] The uv



evidence suggests that like 4-aminoquinazoline, the major site of first protonation of the *lin*-benzoadenines is on the pyrimidine ring. The methylthio derivatives, however, behave similarly to benzimidazole, with the major site of first protonation on the imidazole ring at positions N-1 and N-3.

The favored sites of protonation for the methylthio compound **13** coincide with the favored sites of alkylation (N-1 and N-3) in the presence of potassium carbonate. For *lin*-benzoadenine **1,** however, the favored sites of protonation and alkylation under these conditions do not necessarily coincide. The effect of alkylation at the preferred site of protonation (N-7 or N-5) would require the formulation of imino tautomers or partially quinonoid structures as shown in **37** and **38.** Such structures, in which the electronic system would be highly polarized, would be of relatively high energy, and their formation would require large activation energies. Alkylation at N-1, N-3, or N^8 would not disturb the aromatic system. By analogy to adenine, however, one would expect the N-1 and N-3 positions to be more reactive in the presence of alkali carbonate toward alkylating reageants than the N^8 position.[11] The convenient syntheses of *lin*-benzoadenine **1** by several converging routes, together with the means of establishing the N position of attachment of substituent groups, provide a reliable basis for making a series of linear benzoadenine compounds corresponding to the adenine-containing nucleosides, nucleotides, and, hopefully, polynucleotides and coenzymes.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting apparatus and are corrected. The nmr spectra were recorded on Varian Associates A-60 or A-56/60 spectrometers by Mr. Robert Thrift and his associates using tetramethylsilane (TMS) as an internal standard. The ultraviolet spectra were obtained on a Cary Model 15 spectrophotometer.[12] Microanalyses were performed by Mr. Joseph Nemeth and his associates, who also weighed samples for the quantitative electronic absorption spectra, and by Midwest Microlab, Ltd., Indianapolis, Ind. Mass spectra were obtained on a Varian-MAT CH-5 spectrometer coupled with a 620i computer and Statos recorder by Mr. J. Carter Cook and associates. Infrared spectra were determined on a Perkin-Elmer 337 spectrophotometer. Thin-layer chromatograms were run on Eastman chromagram sheet 6060 (silica gel with fluorescent indicator).

7-Chloro-6-nitro-4-quinazolone (7) and 7-Chloro-8-nitro-4-quinazolone (8). 7-Chloro-4-quinazolone[6] (200 g, 1.11 mol) was added slowly to a cooled solution of concentrated sulfuric acid (400 ml) and fuming nitric acid (400 ml). The resulting solution was heated on a steam bath for 2 hr; then the clear solution was poured into 6 l. of ice water. The resulting pale yellow precipitate was filtered and washed with 4 l. of water. The material was dissolved in hot acetic acid (4.5 l.). Compound **7** crystallized on cooling as bright, yellow prisms (14.4 g, 58%): mp 300–303°; nmr [$(CD_3)_2SO$] δ 3.30 (br, 1, NH), 7.97 (s, 1), 8.28 (s, 1), 8.53 (s, 1); mass spectrum *m/e* (rel intensity) 225 (100) and 227 (36).

Anal. Calcd for $C_8H_4ClN_3O_3$: C, 42.59; H, 1.79; N, 18.63; Cl, 15.72. Found: C, 42.76; H, 1.79; N, 18.85; Cl, 15.68.

The mother liquors were concentrated to 1 l. Upon cooling, a 5:3 mixture (nmr) of **7:8** was recovered (45 g). The material was dissolved in 1 l. of boiling acetic acid. Upon partial cooling to *ca.* 40° colorless crystals of compound **8** were obtained (25 g, 10%): mp >320°; nmr [$(CD_3)_2SO$] δ 7.75 and 8.25 (AB quartet, 2, J = 9 Hz), 8.22 (s, 1); mass spectrum *m/e* (rel intensity) 225 (100) and 227 (36).

Anal. Calcd for $C_8H_4ClN_3O_3$: C, 42.59; H, 1.79; N, 18.63; Cl, 15.72. Found: C, 42.81; H, 1.82; N, 18.50; Cl, 15.72.

7-Amino-6-nitro-4-quinazolone (9). Two sealed tubes, each containing 7-chloro-6-nitro-4-quinazolone (**7,** 12.5 g, 0.056 mol) in ammonis–saturated butanol (80 ml), were heated for 24 hr at 175°. Upon cooling, compound **9** crystallized as yellow-orange needles (total 22.4 g, 98%). Recrystallization from ethanol afforded an analytically pure sample: mp >320°; nmr [$(CD_3)_2SO$] δ 7.20 (s, 1), 7.78 (s, 1), 8.67 (s, 1); mass spectrum *m/e* 206 (M^+).

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.61; H, 2.93; N, 27.18. Found: C, 46.46; H, 2.97; N, 27.08.

6,7-Diamino-4-quinazolone (10). A mixture of 10 g (0.05 mol) of 7-amino-6-nitro-4-quinazolone (**9**) and 1 g of 10% palladium on carbon was stirred in ethanol (150 ml) under nitrogen. A solution of 10 ml of 99% hydrazine hydrate in ethanol (10 ml) was added dropwise over 1 hr longer and then heated ar reflux for another hour. Enough dimethylformamide was added (*ca.* 100 ml) to dissolve the suspended product. The catalyst was removed by filtration and the solvent was removed *in vacuo.* Upon trituration of the residue with water, 7.8 g (91%) of tan-colored product was obtained. An analytical sample was obtained by recrystallization from ethanol: mp >320°; nmr [$(CD_3)_2SO$] δ 6.75 (s, 1), 7.19 (s, 1), 7.72 (s, 1); mass spectrum *m/e* 176 (M^+).

Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.50; H, 4.40; N, 31.60.

Imidazo[4,5-*g*]quinazolin-8-one (11). From 7-Amino-6-nitro-4-quinazolone (9). A mixture of 5 g (25 mmol) of **9** in formic acid (98%, 200 ml) was hydrogenated at 3 atm over 0.5 g of 10% palladium on carbon for 1–2 hr. The catalyst was removed by filtration and the solution was heated at reflux under nitrogen for 2 hr. Removal of the solvent *in vacuo* and reprecipitation of the residue from water with dilute ammonia afforded 2.5 g (54%) of colorless crystalline **11.** An analytical sample could be obtained by recrystallization several times from water: mp >320°; nmr (TFA) δ 8.82 (s, 1), 9.20 (s, 1), 9.46 (s, 1), 9.66 (s, 1); mass spectrum *m/e* 186 (M^+).

Anal. Calcd for $C_9H_6N_4O$: C, 58.06; H, 3.25; N, 30.09. Found: C, 58.13; H, 3.39; N, 30.04.

B. From 6,7-Diamino-4-quinazolone (10). A solution of **10** (33 g, 0.19 mol) in formic acid (500 ml) was heated at reflux under nitrogen for 2 hr. Removal of the solvent *in vacuo* and reprecipitation of the residue from water with dilute ammonia afforded 33 g (94%) of **11** as colorless crystals identical with material prepared in part A (ir and tlc).

8-Mercaptoimidazo[4,5-*g*]quinazoline (12). A mixture of compound **11** (6.5 g, 35 mmol), purified phosphorus pentasulfide (12 g), and 70 ml of dry pyridine was heated at reflux for 24 hr. The solvent was reduced in volume to *ca.* 20 ml, and the solution was poured into 200 ml of boiling water. On cooling, 5.6 g (79%) of **12** was deposited as yellow crystals. An analytical sample was obtained by recrystallization several times from glacial acetic acid: mp >320°; nmr (TFA) δ 8.54 (s, 1), 9.04 (s, 1), 9.34 (s, 1), 9.49 (s, 1); mass spectrum *m/e* 202 (M^+).

Anal. Calcd for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70; S, 15.85. Found: C, 53.28; H, 3.16; N, 26.26; S, 15.85.

8-Aminoimidazo[4,5-*g*]quinazoline (1). A. From 8-Mercaptoimidazo[4,5-*g*]quinazoline (12). A mixture of 7 g (35 mmol) of mercapto compound **12** and 80 ml of ammonia–saturated butanol was heated in a sealed tube at 200° for 48 hr. The crystals were filtered and washed with ethanol to yield 5.4 g (85%) of **1**. The product was dissolved in 150 ml of water by the addition of formic acid and treated with charcoal, and the pH was adjusted to 8 with dilute ammonia. The yield of beige crystals so obtained was 4.5 g (70%). An analytical sample was obtained as the hydrochloride salt (crystallization from water–ethanol–ether): mp >320°; nmr (TFA) δ 8.71 (s, 1), 8.96 (s, 1), 9.26 (s, 1) 9.65 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 237 nm (ϵ 26,500), 242 (26,700), 258 (14,800), 261 (sh), 298 (sh), 318 (6800), 332 (9200), 348 (7000); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 224 nm (ϵ 24,100), 234 (22,800), 258 (12,700), 265 (sh), 289 (sh), 302 (sh), 322 (sh), 333 (14,400), 349 (13,700); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 248 nm (ϵ 36,900), 262 (32,600), 270 (34,100), 310 (sh), 322 (7900), 350 (5900), 365 (sh); mass spectrum *m/e* 185 (M^+ for $C_9H_7N_5$).

Anal. Calcd for $C_9H_8ClN_5$: C, 48.77; H, 3.64; Cl, 15.99; N, 31.60. Found: C, 48.99; H, 3.46; Cl, 16.20; N, 31.79.

B. From 8-Methylthioimidazo[4,5-*g*]quinazoline (13). A mixture of 8.2 g (40 mmol) of methylmercapto compound **13** and 80 ml of ammonia–saturated butanol was heated in a sealed tube at 200° for 24 hr. The yield of crude **1** was 5.3 g (75%), identical with the above material (ir and tlc).

C. From 7-Benzylimidazo[4,5-*g*]quinazoline-8-thione (29). A mixture of **29** (0.2 g, 0.7 mmol) and 4 ml of ammonia–saturated butanol was heated in a sealed tube at 200° for 24 hr. Upon cooling, **1** was deposited as colorless needles (0.127 g, 9%), identical with the other preparations (ir and tlc).

D. From 8-Amino-3-benzylimidazo[4,5-*g*]quinazoline (16). To a stirred suspension of **16** (0.95 g, 4 mmol) in liquid ammonia (30 ml) was added slowly 1 g of sodium (cut in small pieces). The slurry was stirred under reflux for 45 min. At the end of this period, ammonium chloride was added slowly until the deep blue color of the solution disappeared. The reaction mixture was allowed to stand at 25° until the ammonia evaporated. The residue was suspended in water (100 ml) and ether (50 ml) and then filtered to afford an amorphous solid. Recrystallization from acetic acid–ethanol yielded light tan crystals of **1** (0.55 g, 86%), identical with the other preparations (ir and tlc).

8-Methylthioimidazo[4,5-*g*]quinazoline (13). Methyl iodide (0.17 g, 1.2 mmol) was added to a stirred solution of mercapto compound **12** and potassium hydroxide (0.075 g, 1.0 mmol) in methanol (10 ml) and water (10 ml). After stirring at 25° for 15 min, 1 drop of acetic acid was added and the product crystallized slowly. Recrystallization from water–ethanol afforded **13** as pale yellow needles (0.165 g, 79%): mp 311–314°; nmr (TFA) δ 3.10 (s, 3, SCH_3), 8.83 (s, 1), 9.13 (s, 1), 9.22 (s, 1), 9.70 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 240 nm (ϵ 44,500), 284 (7500), 327 (11,600), 341 (10,500), 358 (7600); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 244 nm (ϵ 21,600), 290 (sh), 299 (5200), 344 (13,400), 355 (sh); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 255 nm (ϵ 40,300), 279 (21,200), 323 (sh), 337 (15,900), 364 (sh); mass spectrum *m/e* 216 (M^+).

Anal. Calcd for $C_{10}H_8N_4S$: C, 55.54; H, 3.73; N, 25.91; S, 14.83. Found: C, 55.29; H, 3.65; N, 25.90; S, 14.60.

Alkylation of 8-Methylthioimidazo[4,5-*g*]quinazoline (13). A mixture of **13** (0.4 g, 2 mmol), anhydrous potassium carbonate (0.28 g, 2 mmol), and benzyl bromide (0.34 g, 2 mmol) was stirred at 25° for 10 hr in dry dimethylformamide (20 ml). The reaction mixture was poured into water (150 ml) and upon standing produced a precipitate. This material was filtered, dried, and applied (in acetic acid) to a silica gel column (80 g) packed in chloroform. Elution with chloroform (500 ml) yielded a solution containing mainly 3-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (**14**) (tlc). The solution was evaporated *in vacuo* and the residue was recrystallized from aqueous ethanol to afford **14** (0.235 g, 42%): mp 223–225° (identical with authentic material checked by ir and tlc). Further elution with chloroform (500 ml), then 2% ethanol in chloroform (300 ml), provided a solution containing 1-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (**15**). Evaporation and recrystallization from aqueous ethanol provided this isomer as colorless needles (0.225 g, 41%): mp 211–212°; nmr (TFA) δ 3.05 (s, 3, SCH_3), 5.90 (s, 2, CH_2), 7.52 (s, 5, C_6H_5), 8.00 (s, 1), 8.83 (s, 1), 9.17 (s, 1), 9.48 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 243 nm (ϵ 40,900), 248 (sh), 284 (7500), 323 (9600), 348 (10,200), 366 (8300); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 248 nm (ϵ 22,200), 298 (5200), 348 (14,100); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 243 nm (ϵ 43,800), 248 (sh), 284 (7400), 327 (9900), 348 (10,100), 366 (7700); mass spectrum *m/e* 306 (M^+).

Anal. Calcd for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.61; N, 18.29; S, 10.46. Found: C, 66.80; H, 4.82; H, 18.37; S, 10.53.

3-Benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (14). Methyl iodide (0.17 g, 1.2 mmol) was added to a stirred solution of mercapto compound **24** (0.3 g, 1.0 mmol) and potassium hydroxide (0.1 g, 1.5 mmol) in methanol (10 ml) and water (10 ml). After the solution was stirred at 25° for 13 min, the product precipitated. Crystallization from ethanol provided **14** as colorless needles (0.27 g, 86%): mp 224–225°; nmr (TFA) δ 3.08 (s, 3, SCH_3), 5.87 (s, 2, CH_2), 7.50 (s, 5, C_6H_5), 8.53 (s, 1), 9.12 (s, 1), 9.22 (s, 1), 9.50 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 243 nm (ϵ 56,400), 284 (8800), 329 (13,600), 342 (12,700), 359 (8900); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 252 nm (ϵ 29,800), 289 (6200), 298 (6200), 352 (15,300); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 243 nm (ϵ 59,600), 284 (9700), 329 (13,000), 338 (sh), 359 (8200); mass spectrum *m/e* 306 (M^+).

Anal. Calcd for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.61; N, 18.29; S, 10.46. Found: C, 66.75; H, 4.53; N, 18.07; S. 10.41.

8-Amino-3-benzylimidazo[4,5-*g*]quinazoline (16). A. From 3-Benzyl-8-mercaptoimidazo[4,5-*g*]quinazoline (24). A sealed tube containing the mercapto compound **24** (1.0 g, 3 mmol) and 20 ml of ammonia–saturated ethanol was heated at 150° for 24 hr. Upon cooling, light tan needles of **16** were obtained (0.95 g, 90%). Recrystallization from dimethylformamide afforded analytically pure material (0.70 g, 75%): mp >320°; nmr (TFA) δ 5.83 (s, 2, CH_2), 7.50 (s, 5, C_6H_5), 8.43 (s, 1), 8.95 (s, 1), 9.22 (s, 1), 9.43 (s, 1); $\lambda_{max}^{95\%tOH}$ 231 nm (ϵ 34,300), 242 (sh), 260 (13,000), 266 (13,000), 306 (sh), 319 (6700), 333 (8800), 349 (6700); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 228 nm (ϵ 23,200), 236 (24,100), 263 (12,200), 271 (10,000), 321 (8000), 335 (9500), 351 (8500); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 242 nm (ϵ 26,200), 260 (13,500), 265 (13,500), 306 (sh), 318 (6900), 338 (9000), 349 (7000); mass spectrum *m/e* 275 (M^+).

Anal. Calcd for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44. Found: C, 69.84; H, 4.71; N, 25.63.

B. From 3-Benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (14). A sealed tube containing compound **14** (0.12 g, 0.4 mmol) and 5 ml of ammonia–saturated ethanol was heated at 200° for 24 hr. Upon cooling, light tan needles of **16** were obtained (0.08 g, 75%), identical with the material described above (ir and tlc).

8-Amino-1-benzylimidazo[4,5-*g*]quinazoline (17). A sealed tube containing 100 mg (0.33 mmol) of 1-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (**15**) and 15 ml of ammonia–saturated butanol was heated at 200° for 48 hr. Upon cooling, 25 mg of colorless crystals was deposited. The filtrate was evaporated to dryness *in vacuo*. The resulting residue was crystallized from ethanol to afford colorless crystals of **17** (45 mg, combined yield 78%): mp 295–296°; nmr (TFA) δ 5.88 (s, 2, CH_2), 7.52 (s, 5, C_6H_5), 8.77 (s, 1), 9.15 (s, 1), 9.23 (s, 1), 9.28 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 223 nm (ϵ 26,800), 242 (33,600), 264 (16,000), 295 (5600), 306 (4400), 327 (6200), 343 (9300), 359 (8100); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 237 nm (ϵ 38,300), 264 (19,000), 294 (7700), 306 (6900), 328 (7500), 343 (10,300), 358 (8500); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 236 nm (ϵ 24,200), 267 (12,700), 275 (10,400), 299 (6500), 317 (7690), 328 (sh), 336 (10,100), 352 (9900), 363 (sh); $\lambda_{max}^{0.01\ N\ HCl}$ (95% EtOH) 237 nm (ϵ 27,000), 267 (14,900), 275 (16,600), 313 (10,300), 326.5 (10,000), 343 (9800), 359 (9160); mass spectrum *m/e* 275 (M^+).

Anal. Calcd for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44. Found: C, 69.18; H, 4.78; N, 24.98.

***N*-Benzyl-2-amino-4-benzylamino-5-nitrobenzamide (18).** A solution of 7-chloro-6-nitro-4-quinazolone (1.0 g, 4 mmol) in benzylamine (10 ml) containing 2 drops of concentrated hydrochloric acid was heated at 130° under nitrogen for 24 hr. Upon cooling to room temperature, the product crystallized and was filtered and washed with ethanol (1.0 g, 59%). Recrystallization from

dimethylformamide–ethanol afforded 18 as yellow needles (0.9 g, 53%): mp 209–210°; nmr (TFA) δ 4.17 (s, 4, CH_2), 7.04 (s, 1), 7.33 (s, 10, C_6H_5), 8.87 (s, 1); mass spectrum *m/e* 376 (M^+).

Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.35; N, 14.88. Found: C, 67.09; H, 5.44; N, 14.94.

7-Benzylamino-6-nitro-4-quinazolone (19). A stirred suspension of **7** (10.0 g, 33 mmol) in benzylamine (10 g) and butanol (300 ml) was heated at reflux under nitrogen for 24 hr. Upon cooling, compound **19** was deposited as yellow needles (11.0 g, 81%): mp 172–173°; nmr [$(CD_3)_2SO$] δ 4.68 (d, 2, J = 6 Hz, CH_2), 6.76 (s, 1), 7.35–7.45 (m, 5, C_6H_5), 8.02 (s, 1), 8.76 (s, 1), 8.67 (t, 1, J = 6 Hz, NH); mass spectrum *m/e* 296 (M^+).

Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 61.07; H, 4.15; N, 18.94.

3-Benzyl-7-chloro-6-nitro-4-quinazolone (21). A solution of 7-chloro-6-nitro-4-quinazolone (10 g, 44 mmol), benzyl bromide (7.4 g, 44 mmol), and potassium hydroxide [2.8 g (87%), 44 mmol] in methanol (250 ml) was heated at reflux for 1 hr. Upon cooling, colorless crystals of 21 were collected in two crops (12.4 g, 89%): mp 175–177°. One recrystallization from ethanol afforded analytically pure material: mp 175–177°; nmr (TFA) δ 5.61 (s, 2, CH_2), 7.45 (s, 5, C_6H_5), 8.12 (s, 1), 8.88 (s, 1), 9.28 (s, 1); mass spectrum *m/e* (rel intensity) 315 (100) and 317 (37).

Anal. Calcd for $C_{15}H_{10}CLN_3O_3$: C, 57.07; H, 3.19; Cl, 11.23; N, 13.31. Found: C, 56.79; H, 3.21; Cl, 11.44; N, 13.31.

3-Benzyl-7-benzylamino-6-nitro-4-quinazolone (20). A. From 7-Benzylamino-6-nitro-4-quinazolone (19). Benzyl bromide (0.65 g, 3.8 mmol) was added to a stirred solution of compound **19** (1.1 g, 3.3 mmol) and potassium hydroxide [0.25 g (87%), 3.8 mmol] in methanol (25 ml). The solution was heated under reflux for 1 hr and then cooled to yield **20** as yellow-orange needles (1.2 g, 95%): mp 187–188°; nmr (TFA) δ 4.67 (s, 2, CH_2), 5.37 (s, 2, CH_2), 7.27 (s, 1), 7.33 (s, 5, C_6H_5), 7.42 (s, 5, C_6H_5), 9.18 (s, 1), 9.25 (s, 1); mass spectrum *m/e* 386 (M^+).

Anal. Calcd for $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.69; N, 14.50. Found: C, 68.60; H, 4.79; N, 14.61.

B. From *N*-Benzyl-2-amino-4-benzylamino-5-nitrobenzamide (18). A solution of **18** (0.2 g, 0.5 mmol) in 98% formic acid (15 ml) was heated under reflux for 2 hr. The yellow-orange solution was concentrated *in vacuo* to a small volume and treated with dilute ammonia, affording 0.19 g (93%) of **20**: mp 185–188°, identical with the above material (ir and tlc).

C. From 3-Benzyl-7-chloro-6-nitro-4-quinazolone (21). A solution of **21** (0.5 g, 2 mmol) and benzylamine (0.5 g) in butanol (5 ml) was heated at reflux 18 hr under nitrogen. Upon standing at room temperature, yellow-orange needles of **20** were deposited (0.55 g, 87%): mp 178–187°. Recrystallization from ethanol afforded material identical with the above preparations (ir and tlc): mp 186–188°.

6-Amino-7-benzylamino-4-quinazolone (22). A solution of compound **19** (10 g, 42 mmol) in ethanol (50 ml) and dimethylformamide (150 ml) was hydrogenated at 3 atm over 0.2 g of 5% palladium on carbon for 2 hr at 25°. The solution was filtered and evaporated *in vacuo* to a small volume. Addition of water afforded product **22** as a pink solid (8.5 g, 95%). Two recrystallizations from hot butanol using decolorizing charcoal gave colorless needles; mp 293-295°; nmr (TFA) δ 5.83 (s, 2, CH_2), 7.13 (s, 1), 7.37 (s, 5, C_6H_5), 8.50 (s, 1), 9.15 (s, 1); mass spectrum *m/e* 266 (M^+).

Anal. Calcd for $C_{15}H_{14}N_4O$: 67.65; H, 5.30; N, 21.03. Found: C, 67.43; H, 5.30; N, 20.90.

3-Benzylimidazo[4,5-*g*]quinazolin-8-one (23). A solution of compound **22** (10 g, 0.05 mol) in 98% formic acid (200 ml) was heated under reflux for 90 min. The solution was heated with decolorizing charcoal. Water was added (100 ml) and the solution was evaporated *in vacuo* (*ca.* 50 ml) until the onset of crystallization. Pale yellow crystals were recovered. A second crop was obtained from the mother liquors by neutralization with ammonia (total yield 9.6 g, 93%). One recrystallization from aqueous dimethylformamide gave pale yellow prisms (8.9 g, 86%): mp >320°; nmr (TFA) δ 5.88 (s, 2, CH_2), 7.57 (s, 5, C_6H_5), 8.55 (s, 1), 9.18 (s, 1), 9.48 (s, 1); mass spectrum *m/e* 276 (M^+).

Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; H, 20.28. Found: C, 69.82; H, 4.42; N, 20.28.

3-Benzyl-8-mercaptoimidazo[4,5-*g*]quinazoline (24). A stirred slurry of compound **23** (5.0 g, 20 mmol) and purified phosphorus pentasulfide (8.0 g) in dry pyridine (150 ml) was heated at reflux for 18 hr under nitrogen. The solution was poured into boiling water (800 ml). Upon cooling, bronze-colored needles of 24 were obtained (4.1 g, 78%) which were recrystallized from aqueous dimethylformamide to afford analytically pure material (2.8 g, 53%): mp >320°; nmr (TFA) δ 5.82 (s, 2, CH_2), 7.52 (s, 5, C_6H_5), 8.28 (s, 1), 9.02 (s, 1), 9.22 (s, 1), 9.33 (s, 1); mass spectrum *m/e* 292 (M^+).

Anal. Calcd for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.14; N, 19.16; S, 10.97. Found: C, 65.77; H, 4.33; N, 19.24; S, 11.02.

8-Benzylaminoimidazo[4,5-*g*]quinazoline (25). A sealed tube containing the mercapto compound **12** (0.5 g, 2 mmol), benzylamine (0.5 g), and 15 ml of ethanol was heated at 200°. The solution was filtered and evaporated to dryness. The resulting solid was suspended in water and filtered to yield a pale yellow solid (620 mg, 92%). Recrystallization from ethanol using decolorizing charcoal afforded **25** as colorless needles: mp >320°; nmr [$(CD_3)_2SO$] δ 4.83 (s, 2, CH_2), 7.08–7.50 (m, 5, C_6H_5), 7.86 (s, 1), 8.37 (s, 1), 8.48 (s, 1), 8.65 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 227 nm (ε 38,200), 236 (sh), 264 (13,000), 272 (12,200), 322 (sh), 334 (14,000), 351 (11,300); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 217 nm (ε 34,500), 237 (sh), 265 (7800), 324 (sh), 338 (19,800), 354 (20,900); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 244 nm (ε 42,200), 248 (sh), 270 (sh), 277 (31,400), 324 (12,500), 349 (9500), 365 (7900); mass spectrum *m/e* 275 (M^+).

Anal. Calcd for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44. Found: C, 69.66; H, 4.66; N, 25.33.

7-Amino-3-benzyl-6-nitro-4-quinazolone (26). A sealed tube containing **21** (9.0 g, 30 mmol) and 80 ml of ammonia–saturated ethanol was heated at 150° for 24 hr. Upon cooling, yellow-orange needles of **26** were collected (6.2 g). The mother liquors were concentrated to give a second crop (0.8 g, combined yield 83%): mp 225–227°. Recrystallization from ethanol afforded an analytically pure sample: mp 228–229°; nmr (TFA) δ 5.40 (s, 2, CH_2), 7.30 (s, 1), 7.43 (s, 5, C_6H_5), 9.03 (s, 1), 9.23 (s, 1); mass spectrum *m/e* 296 (M^+).

Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.65; H, 4.14; N, 18.95.

3-Benzyl-6,7-diamino-4-quinazolone (27). A solution of **26** (2.0 g, 7 mmol) in ethanol (100 ml) was hydrogenated at 3 atm over 0.05 g of 5% palladium on carbon during 2 hr at 25°. The solution was filtered and concentrated to *ca.* 30 ml. Water was added and the solution was stored at 4° overnight. Light tan needles of **27** were recovered (1.3 g, 72%): mp 185–193°. The product was dissolved in ethanol, treated with decolorizing charcoal, and diluted with water as above, affording colorless needles: mp 192–193° (slightly hygroscopic); nmr (TFA) δ 5.55 (s, 2, CH_2), 7.27 (s, 1), 7.42 (s, 5, C_6H_5), 8.52 (s, 1), 8.98 (s, 1); mass spectrum *m/e* 266 (M^+).

Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.79; H, 5.35; N, 21.04.

7-Benzylimidazo[4,5-*g*]quinazoline-8-thione (29). A mixture of 6.6 g (24 mmol) of **28**, 24 g of purified phosphorus pentasulfide, and 60 ml of dry pyridine was heated at reflux for 24 hr. The solu- and then diluted with water to a volume of 50 ml. The solution was evaporated to dryness *in vacuo* and the resulting solid was dissolved in hot water. The solution was adjusted to pH 7 with dilute ammonia. Upon cooling, **28** was deposited as colorless crystals (0.425 g, 75%): mp 246–248°. Recrystallization from ethanol afforded an analytically pure sample: mp 248–249°; nmr (TFA) δ 5.55 (s, 2, CH_2), 7.53 (s, 5, C_6H_5), 8.72 (s, 1), 9.20 (s, 1), 9.28 (s, 1), 9.63 (s, 1); mass spectrum *m/e* 276 (M^+).

Anal. Calcd for $C_{16}H_{12}N_40$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.76; H, 4.33; N, 20.61.

7-Benzylimidazo[4,5-*g*]quinazoline-8-thione (29). A mixture of 6.6 g (24 mmol) of **28**, 24 g of purified phosphorus pentasulfide, and 60 ml of dry pyridine was heated at reflux for 24 hr. The solution was poured into boiling water (200 ml), and the yellow precipitate of **29** was collected (5.5 g, 79%). Recrystallization from aqueous dimethylformamide gave an analytical sample: mp 290–291°; nmr [$(CD_3)_2SO$] δ 5.98 (s, 2, CH_2), 7.34 (s, 5, C_6H_5), 7.98 (s, 1), 8.67 (s, 1) 8.78 (s, 1), 9.30 (s, 1); mass spectrum *m/e* 292 (M^+).

Anal. Calcd for $C_{16}H_{12}N_4S$: C, 65.75; H, 4.11; N, 19.17; S, 10.97. Found: C, 65.44; H, 4.25; N, 19.15; S, 11.24.

7-Cyclohexylamino-6-nitro-4-quinazolone (31). A stirred suspension of 7-chloro-6-nitro-4-quinazolone (**7** 5.0 g, 23 mmol) in cyclohexylamine (5.0 g) and butanol (150 ml) was heated at reflux under nitrogen for 16 hr. The resulting solution was poured slowly into 1.5 l. of boiling water. Upon cooling, yellow-orange needles of **31** separated (6.1 g, 90%): mp 263–265°; nmr (TFA) δ 1.4–2.3 (br, 11, C_6H_{11}), 7.27 (s, 1), 9.25 (s, 1), 9.28 (s, 1); mass spectrum *m/e* 288 (M^+).

Anal. Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.19; H, 5.75; N, 19.29.

6-Amino-7-cyclohexylamino-4-quinazolone (32). A solution of **31** (2.0 g, 7 mmol) in ethanol (35 ml) and dimethylformamide (35 ml) was hydrogenated at 3 atm over 0.05 g of 5% palladium on

carbon during 1 hr at 25°. The solution was filtered and evaporated to a small volume. Addition of water afforded 1.7 g of a colorless solid (95%). Recrystallization from ethanol yielded **32** as colorless needles (1.5 g, 84%). One further recrystallization afforded an analytically pure sample: mp >320°; nmr (TFA) δ 1.3–2.3 (br, 11, C_6H_{11}), 7.18 (s, 1), 8.42 (s, 1), 9.20 (s, 1); mass spectrum *m/e* 258 (M^+).

Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 64.92; H, 6.86; N, 21.51.

3-Cyclohexylimidazo[4,5-*g*]quinazolin-8-one (33). A solution of **32** (0.85 g, 3.0 mmol) in 98% formic acid (50 ml) was heated at reflux for 1 hr. The reaction mixture was treated with decolorizing charcoal, diluted with water (50 ml), and concentrated *in vacuo* to a small volume. Dilute ammonia was added to afford **33** as a colorless powder (0.75 g, 85%). Two recrystallizations from ethanol yielded colorless prisms: mp 268–270°; nmr [$(CD_3)_2SO$] δ 1.2–2.2 (br, 11, C_6H_{11}), 7.90 (s, 1), 8.01 (s, 1), 8.40 (s, 1), 8.55 (s, 1); mass spectrum *m/e* 268 (M^+).

Anal. Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.28. Found: C, 67.19; H, 5.95; N, 20.57.

3-Cyclohexyl-8-mercaptoimidazo[4,5-*g*]quinazoline (34). A stirred slurry of **33** (0.75 g, 3 mmol) and purified phosphorus pentasulfide (1.5 g) in dry pyridine (50 ml) was heated 12 hr under reflux. The resulting dark solution was poured into boiling water (600 ml). Upon cooling, **34** separated as a pale yellow precipitate (0.55 g, 69%). Two recrystallizations from acetic acid–ethanol yielded yellow prisms: mp >320°; nmr [$(CD_3)_2SO$] δ 1.2–2.2 (br, 11, C_6H_{11}), 8.08 (s, 1), 8.13 (s, 1), 8.80 (s, 1), 8.90 (s, 1); mass spectrum *m/e* 284 (M^+).

Anal. Calcd for $C_{15}H_{16}N_4S$: C, 63.35; H, 5.67; N, 19.70; S, 11.27. Found: C, 63.09; H, 5.76; N, 19.57; S, 11.45.

8-Amino-3-cyclohexylimidazo[4,5-*g*]quinazoline (30). A sealed tube containing **34** (0.1 g, 0.4 mmol) and 3 ml of ammonia–saturated ethanol was heated at 150° for 24 hr. Upon cooling, colorless needles of **30** were deposited (0.8 g, 85%). Recrystallization from hot dimethylformamide afforded analytically pure **30**: mp >320°; nmr [$(CD_3)_2SO$] δ 1.2–2.2 (br, 11, C_6H_{11}), 8.62 (s, 1), 9.04 (s, 1), 9.44 (s, 1), 9.56 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 231 nm (ε 46,700), 242 (sh), 260 (sh), 266 (17,100), 307 (sh), 319 (9100), 334 (11,700), 351 (9100); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 225 nm (ε 32,500), 233 (sh), 260 (13,600), 266 (sh), 307 (sh), 322 (10,200), 336 (13,400), 352 (12,600); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 242 nm (sh), 260 (ε 18,000), 266 (sh), 307 (sh), 319 (9500), 334 (12,000), 351 (9500); mass spectrum *m/e* 267 (M^+).

Anal. Calcd for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.30; H, 6.45; N, 25.96.

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Registry No.—**1**, 53449-12-0; 1 HCl, 53449-13-1; **6**, 31374-18-2; **7**, 53449-14-2; **8**, 53449-15-3; **9**, 53449-16-4; **10**, 53449-17-5; **11**, 53449-18-6; **12**, 53449-19-7; **13**, 53449-20-0; **14**, 53449-21-1; **15**, 53449-22-2; **16**, 53449-23-3; **17**, 53449-24-4; **18**, 53449-25-5; **19**, 53449-26-6; **20**, 53449-27-7; **21**, 53449-28-8; **22**, 53449-29-9; **23**, 53449-30-2; **24**, 53449-31-3; **25**, 53449-32-4; **26**, 53449-33-5; **27**, 53449-34-6; **28**, 53449-35-7; **29**, 53449-36-8; **30**, 53449-37-9; **31**, 53449-38-0; **32**, 53449-39-1; **33**, 53449-40-4; **34**, 53449-41-5; benzyl bromide, 100-39-0; benzylamine, 100-46-9; cyclohexylamine, 108-91-8.

References and Notes

(1) (a) For example, see R. K. Robins, *J. Med. Chem.*, **7**, 186 (1964); (b) R. K. Robins, *Heterocycl. Compounds*, **8**, 162 (1967); (c) J. A. Montgomery, T. P. Johnson, and Y. F. Sheely in "Medicinal Chemistry," Part 1, 3rd ed, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970; (d) D. Cole, University of Illinois Seminar Abstracts, Dec 14, 1972.
(2) The prefix *lin* refers to the linear disposition of the three rings in compound **1**; *prox* for proximal and *dist* for distal refer to the relationship of the amino group in compounds **2** and **3**, respectively, with respect to the imidazole ring. The numbering of the three ring systems is as shown.
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(11) J. H. Lister, *Chem. Heterocycl. Compounds*, **30**, 342 (1971).
(12) For uv spectra not recorded, consult the Ph.D. dissertation of A. G. Morrice, University of Illinois, 1974.

The Angular Benzoadenines. 9-Aminoimidazo[4,5-*f*]quinazoline and 6-Aminoimidazo[4,5-*h*]quinazoline

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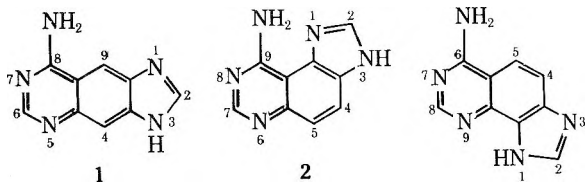
The synthesis of 9-aminoimidazo[4,5-*f*]quinazoline (**2**) and 6-aminoimidazo[4,5-*h*]quinazoline (**3**), angular benzologs of adenine which are given the descriptive names *prox*-benzoadenine and *dist*-benzoadenine, respectively, is reported. The proximal isomer of benzoadenine **2** is synthesized in several steps from 6-acetamido-4-quinazolone (**14**). The distal isomer of benzoadenine **3** is prepared *via* a related route from 7-chloro-8-nitro-4-quinazolone (**4**). The uv spectra of the *lin*-, *prox*-, and *dist*-benzoadenines are discussed in relation to the differing spatial arrangements of the three isomers.

We have undertaken the synthesis of a family of structural analogs of adenine in which a benzene ring has been "inserted" between the imidazole and pyrimidine moieties to form a "stretched-out" purine model. In the preceding paper,[1] we discussed the synthesis and chemical properties of the linearly extended analog, 8-aminoimidazo[4,5-*g*]quinazoline (**1**) for which we proposed the name *lin*-benzoadenine. In this paper we describe the synthesis of the two angular isomers of *lin*-benzoadenine, 9-aminoimidazo[4,5-*f*]quinazoline (**2**) and 6-aminoimidazo[4,5-*h*]quinazoline (**3**), for which we propose the descriptive names, *prox*-benzoadenine (**2**) and *dist*-benzoadenine, respectively.[2]

The similarity of the three isomeric benzoadenines (**1**–**3**) lies in the fact that they contain binding sites similar to the $1,N^6$ binding sites found in adenine and related nucleosides and nucleotides. The differences reside (a) in the spatial re-



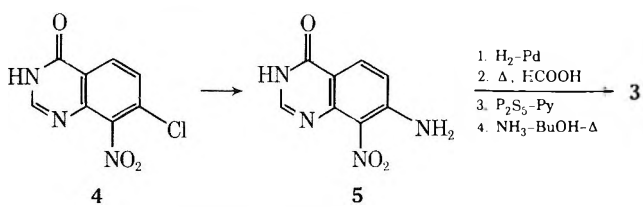
1 2 3

lationships of the pyrimidine and imidazole rings with respect to the central benzene ring and (b) in the extent to which internal hydrogen bonding is likely to occur in the three isomers. The structural differences may help elucidate the geometrical restraints placed upon the utilization of adenine benzologs as surrogates for naturally occurring adenine derivatives in biological systems.

The synthetic method utilized for the preparation of **2** and **3** was modeled after that employed for the synthesis of *lin*-benzoadenine (**1**).[1] The construction of the heterocyclic system contained in the angular compounds **2** and **3** was effected *via* the annelation of an imidazole ring onto a disubstituted quinazoline.

Results and Discussion

The nitration of 7-chloro-4-quinazolone,[3] as described in the previous paper, gave a mixture of two isomeric chloronitroquinazolines. The minor isomer, 7-chloro-8-nitro-4-quinazolone (**4**), was heated with ammonia-saturated butanol in a sealed tube to afford the corresponding amine **5**. Compound **5** was hydrogenated in formic acid to generate the diamino compound, and subsequent heating of the reaction mixture produced the tricyclic imidazoquinazolone. Treatment with phosphorus pentasulfide in refluxing pyridine led to the isolation of 6-mercaptoimidazo[4,5-*h*]quinazoline. The thiation proceeded slowly, requiring 3 days for complete reaction, apparently due to the intermediate formation of an insoluble complex between phosphorus pentasulfide and imidazo[4,5-*h*]quinazolin-6-one. The mercapto compound was then converted to *dist*-benzoadenine, 6-aminoimidazo[4,5-*h*]quinazoline (**3**), by treatment with ammonia-saturated butanol.



4 5

For the preparation of the proximal isomer of benzoadenine (**2**), it was anticipated that 6-chloro-4-quinazolone (**6**)[4] could be used as a starting material in a route to **2** analogous to that described above. Nitration of **6** yielded a single product, 6-chloro-5-nitro-4-quinazolone (**7**) as shown by the nmr spectrum, but reaction of **7** with ammonia in butanol at 175° led to displacement of nitro rather than chloro, with the formation of 5-amino-6-chloro-4-quinazolone (**8**). Conversion of the activated 5-carbon from sp^2 to sp^3 in the transition state must be accompanied by sufficient relief of steric compression between the nitro and the coplanar adjacent carbonyl and chloro groups as to supervene over the $sp^2 \rightarrow sp^3$ conversion at the competing activated 6-carbon. By contrast, coplanarity of the amino group with the adjacent carbonyl and chloro groups will be energetically favored in the product **8**. Since further nucleophilic displacement of the 6-chloro substituent of **8** seemed unfavorable, a modified approach was adopted.

Nitration of 6-acetamido-4-quinazolone (**9**)[5] gave 6-acetamido-5-nitro-4-quinazolone (**10**) as the sole product. The acetamido function was hydrolyzed to the corresponding

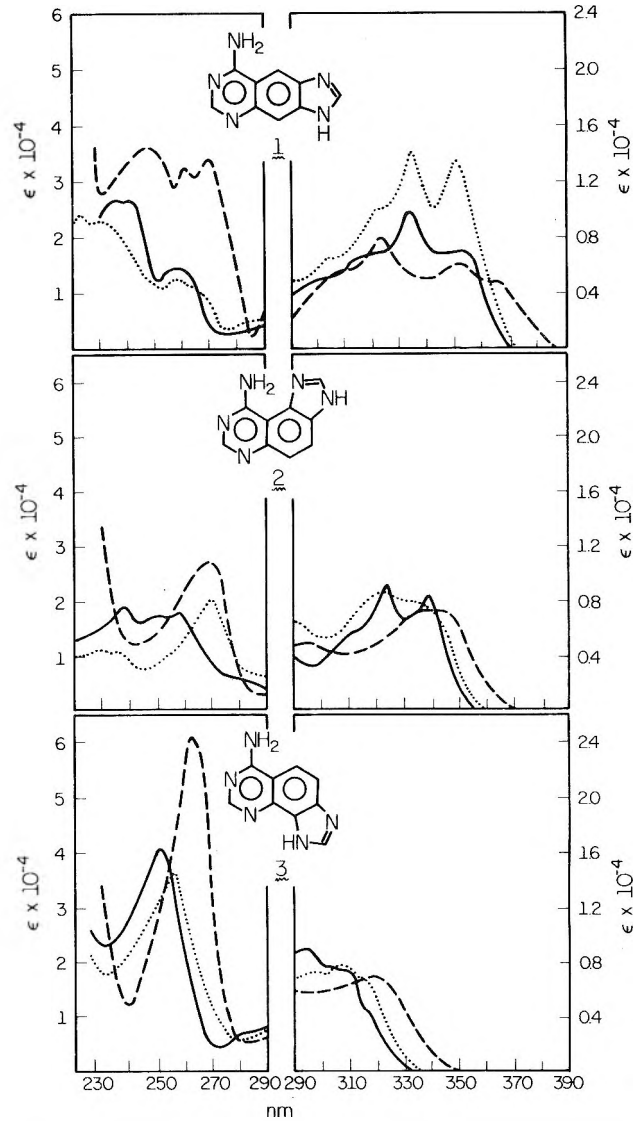
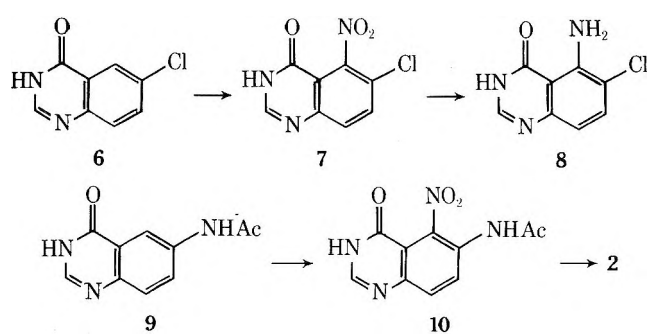


Figure 1. The uv spectra of *lin*-, *prox*-, and *dist*-benzoadenine in 95% ethanol (———), 0.1 *N* HCl in 95 ethanol (·····), and 0.1 *N* NaOH in 95% ethanol (- - - - -).

amine with dilute hydrochloric acid. Reduction of the nitro group and subsequent condensation of the diamino intermediate with formic acid afforded imidazo[4,5-*f*]quinazolin-9-one. Thiation with phosphorus pentasulfide in pyridine yielded 9-mercaptoimidazo[4,5-*f*]quinazoline which was converted to *prox*-benzoadenine, 9-aminoimidazo[4,5-*f*]quinazoline (**2**), by heating in ammonia-saturated butanol. The final conversion could also be effected by treatment with hydrazine followed by hydrogenolysis.[6]



6 7 8

9 10

The ultraviolet spectra of benzoadenines **1**–**3** are shown in Figure 1. In general, the spectra of heteraromatic compounds can usually be related to absorption properties of their carbocyclic analogs.[7] Accordingly, *lin*-benzoadenine **1**

is formally related to anthracene; the angular benzoadenines **2** and **3** can be related to phenanthrene. Aromatic systems of the linear type (such as **1**) generally exhibit lower energy electronic transitions than isomers of the angular type (such as **2** and **3**).[8] Thus, the low energy bands for the distal isomer **3** are shifted 30 nm to shorter wavelength relative to the corresponding bands for *lin*-benzoadenine (**1**), and those for the proximal isomer **2** exhibit a hypsochromic shift of 10 nm relative to **1**. It is apparent that a countering bathochromic effect is occurring in the latter isomer; otherwise the shift would have been expected to be greater, *i.e.*, closer to that for **3**, namely 30 nm. Accordingly, one looks for a unique structural basis in **2** to account for the comparative electronic absorption data. In compound **2**, intramolecular hydrogen bonding between N^9 and N-1 will assist in maintaining the NH_2 group coplanar with the heterocyclic ring system, thereby extending the π-electron system and lowering the excitation energy, whereas in compounds **1** and **3**, the steric interaction between NH_2 and the peri hydrogen (8-NH_2 and 9-H for **1**; 6-NH_2 and 5-H for **3**) tends for force the NH_2 out of coplanarity, resulting in less effective overlap between the lone pair electrons and the π system. Among the three benzoadenines, *prox*-benzoadenine **2** is the most ready to give up its imidazole hydrogen, exhibiting a pK_a in 66% dimethylformamide of 11.4, while *dist*-benzoadenine **3** is least ready to give up its imidazole hydrogen, with a pK_a of 12.25, and *lin*-benzoadenine **1** is intermediate, pK_a = 11.7. This pattern is consistent with stabilization by intramolecular hydrogen bonding of the anion of **2** and of the free base **3**. In addition, the latter (**3**) is also the least ready to protonate, pK_a 4.9, *vs.* 5.2 for isomer **2** and 5.6 for isomer **1**.

In sequels we shall discuss the ribosidation and the preparation of further substituted derivatives of the benzoadenines to test various concepts concerning structure and biological activity.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting apparatus and are corrected. The nmr spectra were recorded on Varian Associates A-60 or A-56/60 spectrometers by Mr. Robert Thrift and his associates using tetramethylsilane (TMS) as an internal standard. The ultraviolet spectra were obtained on a Cary Model 15 spectrophotometer.[9] Microanalyses were performed by Mr. Joseph Nemeth and his associates, who also weighed samples for the quantitative electronic absorption spectra, and by Midwest Microlab, Inc., Indianapolis, Ind. Mass spectra were obtained on a Varian-MAT CH-5 spectrometer coupled with a 620i computer and Statos recorder by Mr. J. Carter Cook and associates. Infrared spectra were determined on a Perkin-Elmer 337 spectrophotometer. Thin-layer chromatograms were run on Eastman Chromagram Sheet 6060 (silica gel with fluorescent indicator).

7-Amino-8-nitro-4-quinazolone (5). A sealed tube containing **4** (1 g, 4.5 mmol) and ammonia-saturated methanol was heated at 175° for 24 hr. Reduction in volume until the appearance of a precipitate and cooling yielded 0.8 g of 7-amino-8-nitro-4-quinazolone (**5**, 87%). Recrystallization several times from ethanol afforded an analytical sample: mp 293–295°; nmr [$(CD_3)_2SO$] δ 6.79 (s, 2, disappears on D_2O shake, NH_2), 6.99 and 7.90 (AB quartet, 2, J = 9 Hz), 8.05 (s, 1); mass spectrum m/e 206 (M^+).

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.61; H, 2.93; N, 27.18. Found: C, 46.57; H, 3.03; N, 26.91.

Imidazo[4,5-*h*]quinazolin-6-one. A solution of **5** (6.6 g, 32 mmol) in formic acid (150 ml) was hydrogenated over 0.6 g of 10% palladium on carbon at 3 atm for 3 hr. After removal of the catalyst by filtration, the solution was refluxed under nitrogen for 2 hr. About 50 ml of water was added, and the volume of the solution was reduced until a white precipitate appeared. On cooling, 4.7 g of white crystals of imidazo[4,5-*h*]quinazolin-6-one was obtained. The mother liquor, on adjustment to pH 8 with ammonia, afforded a further 0.1 g (total 4.8 g, 81%). An analytical sample was obtained by recrystallization several times from water: mp >320°; nmr (TFA) δ 8.14 and 8.74 (AB quartet, 2, J = 9 Hz), 9.37 (s, 1), 9.60 (s, 1); mass spectrum m/e 186 (M^+).

Anal. Calcd for $C_9H_6N_4O$: C, 58.06; H, 3.25; N, 30.09. Found: C, 58.15; H, 3.30; N, 30.25.

6-Mercaptoimidazo[4,5-*h*]quinazoline. A slurry of imidazo[4,5-*h*]quinazolin-6-one (1 g, 5.4 mmol) and phosphorus pentasulfide (5.0 g) in dry pyridine (50 ml) was heated at reflux under nitrogen for 72 hr. After 24 hr the mixture had become clear. The orange solution was poured into hot water (175 ml) and allowed to stand, with the separation of yellow crystals (0.76 g, 70%). Recrystallization from acetic acid–dimethylformamide afforded pale yellow crystals: mp >320°; nmr (TFA) δ 8.17 and 8.92 (AB quartet, 2, J = 9 Hz), 9.00 (s, 1), 9.47 (s, 1); mass spectrum m/e 202 (M^+).

Anal. Calcd for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70; S, 15.85. Found: C, 53.51; H, 3.25; N, 27.88; S, 15.84.

6-Aminoimidazo[4,5-*h*]quinazoline (3). A sealed tube containing 6-mercaptoimidazo[4,5-*h*]quinazoline (0.1 g, 0.6 mmol) and ammonia-saturated butanol (10 ml) was heated at 200° for 24 hr. The reaction mixture was filtered, and the crystals were dissolved in water by the addition of formic acid and reprecipitated with ammonia to yield 0.056 g (50%) of **3** as a white powder. Recrystallization from acetic acid–ethanol gave analytically pure white crystals: mp >320°; nmr [$(CD_3)_2SO$] δ 7.80 and 8.42 (AB quartet, 2, J = 9 Hz), 8.28 (s, 1), 8.42 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 251 nm (ϵ 40,700), 280 (sh), 295 (9000), 303 (sh), 309 (sh), 315 (sh); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 255 (35,700), 295 (sh), 307 (7700), 315 (sh); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 262 (61,200), 320 (6900); mass spectrum m/e 185 (M^+).

Anal. Calcd for $C_9H_7N_5$: C, 58.37; H, 3.81; N, 37.82. Found: C, 58.10; H, 3.84; N, 37.75.

6-Chloro-5-nitro-4-quinazolone (7). A mixture of 6-chloro-4-quinazolone (**6**,[4] 5 g, 28 mmol), 10 ml of fuming nitric acid, and 10 ml of concentrated sulfuric acid was heated on a steam bath for 3 hr. When the mixture was poured into ice water, 3.4 g of crude yellow material was obtained. Recrystallization from acetic acid afforded 1.5 g of **7** as white crystals. Reduction in volume yielded a second crop (0.1 g, total 1.6 g, 26%): mp 308°; nmr [$(CD_3)_2SO$] δ 7.83 and 8.10 (AB quartet, 2, J = 9 Hz), 8.23 (s, 1, 2-H); mass spectrum m/e (rel intensity) 225 (100) and 227 (36).

Anal. Calcd for $C_8H_4ClN_3O_3$: C, 42.49; H, 1.79; Cl, 15.72; N, 18.63. Found: C, 42.67; H, 1.91; Cl, 15.60; N, 18.55.

5-Amino-6-chloro-4-quinazolone (8). A sealed tube containing compound **7** (5 g, 22 mmol) and ammonia-saturated butanol (70 ml) was heated at 175° for 24 hr. The crystals that separated during the course of the reaction were collected and dried to give 3.6 g (83%) of **8**: mp 278–279°; nmr [$(CD_3)_2SO$] δ 6.72 and 7.55 (AB quartet, 2, J = 9 Hz), 7.19 (br s, disappears on D_2O shake, NH_2), 7.95 (s, 1); mass spectrum m/e (rel intensity) 195 (100) and 197 (36).

Anal. Calcd for $C_8H_6ClN_3O$: C, 49.12; H, 3.09; Cl, 18.21; N, 21.48. Found: C, 49.06; H, 2.98; Cl, 18.24; N, 21.51.

6-Acetamido-5-nitro-4-quinazolone (10). 6-Acetamido-4-quinazolone (**9**,[5] 10 g, 48 mmol) was added to a mixture of red fuming nitric acid (100 ml) and concentrated sulfuric acid (100 ml) in portions such that the temperature did not exceed 10°. The solution was stirred 30 min longer at 0–10° and then poured into 1 l. of ice water. After refrigeration for several hours, yellow crystals of **10** deposited and were recrystallized from water (500 ml) to give 5.9 g (40%) of pure material: mp 311–312° dec; nmr [$(CD_3)_2SO$] δ 2.11 (s, 3, $COCH_3$), 7.84 and 8.08 (AB quartet, 2, J = 9 Hz), 8.20 (s, 1, 2-H); mass spectrum m/e 248 (M^+).

Anal. Calcd for $C_{10}H_8N_4O_4$: C, 48.39; H, 3.25; N, 22.57. Found: C, 48.33; H, 3.07; N, 22.72.

6-Amino-5-nitro-4-quinazolone. A mixture of *N*-acetyl derivative **10** (0.1 g, 0.4 mmol) and 10 ml of 1 *N* HCl was heated at reflux under nitrogen for 2 hr. The solution was reduced in volume and, upon cooling, red crystals were deposited and recrystallized from aqueous ethanol (0.064 g, 75%): mp 310–311°; nmr [$(CD_3)_2SO$] δ 7.28 and 7.60 (AB quartet, 2, J = 8 Hz), 8.14 (s, 1, 2-H); mass spectrum m/e 206 (M^+).

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.61; H, 2.93; N, 27.18. Found: C, 46.64; H, 2.88; N, 27.05.

Imidazo[4,5-*f*]quinazolin-9-one. A mixture of 6-amino-5-nitro-4-quinazolone (3 g, 16 mmol) and formic acid (100 ml) was hydrogenated over 0.3 g of 10% palladium on carbon at 3 atm for 30 min. The catalyst was removed by filtration, and the solution was heated at reflux under nitrogen for 2 hr. The solvent was removed *in vacuo*. The residue was dissolved in water (30 ml), the pH was adjusted to 8 with dilute ammonia, and the solution was chilled. The white crystals were deposited and recrystallized from

water (2.0 g, 69%): mp >320°; nmr (TFA) δ 8.22 and 8.63 (AB quartet, 2, J = 9 Hz), 10.92 (s, 1), 10.97 (s, 1); mass spectrum m/e 186 (M^+).

Anal. Calcd for $C_9H_6N_4O$: C, 58.06; H, 3.25; N, 30.09. Found: C, 58.06; H, 3.44; N, 30.00.

9-Mercaptoimidazo[4,5-*f*]quinazoline. Phosphorus pentasulfide (2.4 g) was dissolved in pyridine (36 ml) with heating, 0.6 g (3 mmol) of imidazo[4,5-*f*]quinazolin-9-one was added, and the mixture was heated at reflux for 17 hr. The volume was reduced to 12 ml by removal of the solvent *in vacuo*, and the solution was poured into boiling water (500 ml). The yellow crystals that were deposited were recrystallized from aqueous dimethyl sulfoxide (0.5 g, 78%): mp >320°; nmr (TFA) δ 8.15 and 8.56 (AB quartet, 2, J = 9 Hz), 10.63 (s, 1), 10.91 (s, 1); mass spectrum m/e 202 (M^+).

Anal. Calcd for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70; S, 15.85. Found: C, 53.69; H, 3.00; N, 27.47; S, 15.91.

9-Aminoimidazo[4,5-*f*]quinazoline (2). A. *Via* 9-Hydrazinoimidazo[4,5-*f*]quinazoline. A solution of 9-mercaptoimidazo[4,5-*f*]quinazoline (1 g, 5 mmol) in hydrazine hydrate (6 ml) and methyl cellosolve (4 ml) was heated at 100° for 2 hr. The reaction mixture was poured into ethanol (20 ml) and upon cooling, tan crystals of 9-hydrazinoimidazo[4,5-*f*]quinazoline were obtained (1 g, 100%): mp 225° dec; mass spectrum m/e 200 (M^+). The hydrazino derivative was dissolved in hot methyl cellosolve (300 ml), and the solution was refluxed for 2 hr with addition of 2-ml portions of Raney nickel suspension every 20 min. The catalyst was removed by filtration, and the volume was reduced to 40 ml. Upon cooling, tan crystals of **2** were obtained (0.336 g, 37%). Recrystallization from ethanol yielded an analytical sample: mp >320°; nmr [$(CD_3)_2SO$] δ 7.73 and 8.25 (AB quartet, 2, J = 9 Hz), 8.72 (s, 1), 8.82 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 238 nm (ε 19,000), 251 (17,300), 258 (18,000), 278 (sh), 312 (5900), 324 (9300), 335 (sh), 339 (8500); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 229 (11,000), 237 (10,800), 270 (20,500), 290 (sh), 324 (8600), 335 (sh); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 269 (27,700), 296 (4900), 333 (7600), 346 (sh); mass spectrum m/e 185 (M^+).

Anal. Calcd for $C_9H_7N_5$: C, 58.37; H, 3.81; N, 37.82. Found: C, 58.20; H, 3.91; N, 37.53.

B. From 9-Mercaptoimidazo[4,5-*f*]quinazoline. A sealed tube containing the mercapto compound (0.5 g, 2.5 mmol) and ammonia-saturated butanol (20 ml) was heated at 220° for 24 hr. The crystals were filtered and dissolved in water (10 ml) by the addition of formic acid. Upon adjusting to pH 8 with ammonia, *prox*-benzoadenine was obtained as colorless crystals (0.38 g, 67%), identical with material synthesized in part A (ir, tlc).

pK_a Determinations. In 66% dimethylformamide (34% water) the following pK_a values were observed: *lin*-benzoadenine (**1**), 5.6, 11.7; *prox*-benzoadenine (**2**), 5.2, 11.4; *dist*-benzoadenine (**3**), 4.9, 12.25.

Acknowledgment. This work was supported by Research Grant GM 05829 from the National Institutes of Health. The mass spectral data processing equipment employed in the present study was provided by Research Grants CA 11388 and GM 16864, from the National Cancer Institute and the National Institute of General Medical Sciences, respectively, of the National Institutes of Health, U. S. Public Health Service. We thank Mary Ann Bogan and George Maciak of the Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind., for the pK_a determinations.

Registry No.—**2**, 53449-43-7; **3**, 53449-44-8; **4**, 53449-15-3; **5**, 53449-45-9; **6**, 16064-14-5; **7**, 53449-46-0; **8**, 53449-47-1; **9**, 16064-11-2; **10**, 53449-48-2; imidazo[4,5-*h*]quinazolin-6-one, 53449-49-3; 6-mercaptoimidazo[4,5-*h*]quinazoline, 53449-50-6; 6-amino-5-nitro-4-quinazolone, 53449-51-7; imidazo[4,5-*f*]quinazolin-9-one, 53449-52-8; 9-mercaptoimidazo[4,5-*f*]quinazoline, 53449-53-9; 9-hydrazinoimidazo[4,5-*f*]quinazoline, 53500-17-7.

References and Notes

(1) N. J. Leonard, A. G. Morrice, and M. A. Sprecker, *J. Org. Chem.*, preceding paper.
(2) The prefix *lin* refers to the linear relationships of the three rings in compound **1**; *prox* for proximal and *dist* for distal refer to the spatial relationship of the amino group in compounds **2** and **3**, respectively, with respect to the imidazole ring. The term "benzo" presents no ambiguity for only when the ring is central does it contain no nitrogens and is accordingly "benzo."
(3) C. C. Price, N. J. Leonard, and D. Y. Curtin, *J. Amer. Chem. Soc.*, **68**, 1305 (1946).
(4) M. M. Endicott, B. W. Alden, and M. L. Sherril, *J. Amer. Chem. Soc.*, **68**, 1303 (1946).
(5) R. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. W. Williams, *J. Org. Chem.*, **17**, 141 (1952).
(6) This method of effective SH to NH_2 conversion was developed by M. Saneyoshi and K. Terashima, *Chem. Pharm. Bull.*, **17**, 2373 (1969).
(7) E. Clar, "The Aromatic Sextet," Wiley, New York, N.Y., 1972.
(8) H. H. Jaffé and M. Orchin, "Theory and Application of Ultraviolet Spectroscopy," Wiley, New York, N.Y., 1962, pp 345–375.
(9) For uv spectra not recorded, consult the Ph.D. dissertation of A. G. Morrice, University of Illinois, 1974.

Cyclization of 1-Acetylanthraquinone[1]

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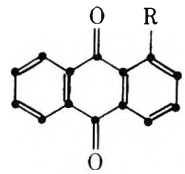
1-Acetylanthraquinone (**1b**) cyclizes under alkaline conditions to give 1-methoxy-2,6-aceanthrylenedione (**2b**). The mechanism of the reaction is discussed.

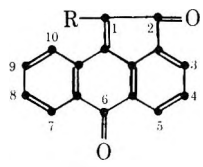
Anthraquinone (**1a**) is, of course, the parent substance of an extensive family of polycyclic quinones,[2] but one of the simplest possible members of the family, 2,6-aceanthrylenedione (**2a**), has never been prepared. This is simply a cyclic vinylog of anthraquinone and, as such, might be capable of reversible reduction to the dihydro or "vat" form (**3**), corresponding to anthrahydroquinone (**4**).

We have attempted the synthesis of **2a** by cyclodehydration of 1-acetylanthraquinone (**1b**), but this reaction does not succeed under a variety of acidic and basic conditions that were tried. The cyanoacetyl derivative (**1c**) might be expected to cyclize more easily, but we were unable to prepare this compound in working quantities. Bromination of **1b** to **1d** proceeded smoothly, but replacement of Br by CN did not.

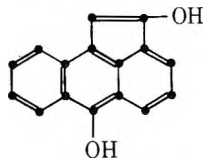
We then found that **1b** is readily cyclized in dimethyl sulfoxide containing "Triton B." The product is not, indeed, **2a**, but (as shown by analysis and molecular weight determination) a methoxy derivative of it, and since oxidation of this product gives a mixture of 1-anthraquinonecarboxylic acid (**1e**) and the glyoxylic ester (**1f**), it is evidently the 1-methoxy derivative (**2b**). Two other structures (**5b** and **6b**) can be written for a methoxyaceanthrylenedione capable of oxidation to **1e**, but neither system is a plausible cyclization product of **1b**, and neither would be capable of oxidation to **1f**. In addition, we have synthesized isomer **5b**



1a, R = H
b, R = $COCH_3$
c, R = $COCH_2CN$
d, R = $COCH_2Br$
e, R = COOH
f, R = $COCOOCH_3$
g, R = $COCHBr_2$



2a, R = H
b, R = CH_3O
c, R = OH



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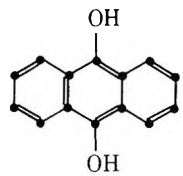

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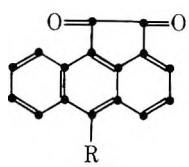
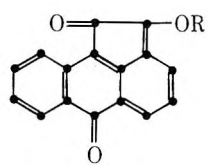
and found it to be different from **2b**. The synthesis is based upon our finding that 1,2-aceanthrylenedione **5a**[3] brominates cleanly in the 6-position to give **5c** (as shown by oxidation to **1e**), which readily gives **5b** by methanolysis. (Piperidine gives **5d**.)

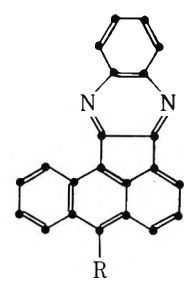
The 1,2-dione structures of **5a–d** are confirmed by their rapid condensation with o-phenylenediamine, eliminating two molecules of water to give quinoxalines **7a–d**, respectively; these are convenient derivatives for characterization purposes. The 2,6-dione (**2b**) does not react in this way.



5a, R = H
b, R = CH_3O
c, R = Br
d, R = $(CH_2)_5N$



6a, R = H
b, R = CH_3



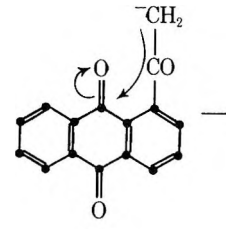
7a, R = H
b, R = CH_3O
c. R = Br
d, R = $(CH_2)_5N$

In our view, the most plausible explanation for the formation of **2b** from **1b** is that the expected product (**2a**) does form but is not stable under the reaction conditions; instead it undergoes nucleophilic methoxylation. The first step of the reaction is evidently loss of a proton from **1b** to form the anion (**8**), followed by cyclization to anion **9**. Proton transfer then gives the resonance stabilized **10**, which can eliminate hydroxyl to form the fully conjugated **2a**. Methoxide attack at the 1-position then gives **11**, converted to **2b** by hydride elimination under the influence of atmospheric oxygen.

Under similar conditions, 1,5-diacetylanthraquinone (**12**) cyclizes once, giving **13**.

Liebermann and Kardos reported in 1914[4] that boiling KOH attacked **5a** to give a hydroxyl derivative, formulated as **2c** or its tautomer (**6a**), which formed a dark red methyl ether of mp 233°. These properties correspond to those of **2b**, but an attempt to repeat these experiments gave equivocal results, unfortunately, so that it has not been possible to make a direct comparison.

1-Acetylanthraquinone (**1b**), which reacts with hydrazine to give the dibenzocinnolone (**14**), behaves normally on alkaline hydrosulfite reduction, *i.e.*, it gives a deep red solu-



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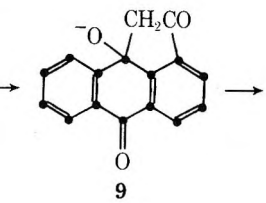

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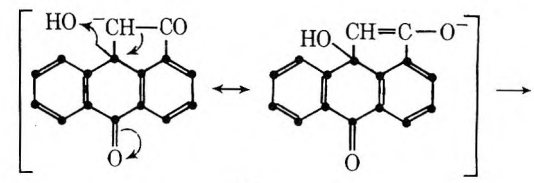

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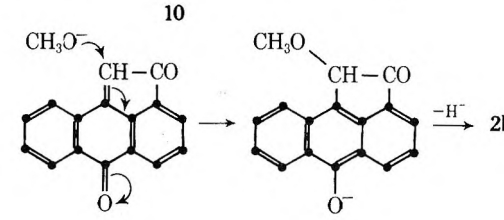
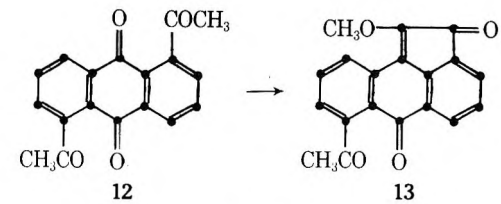
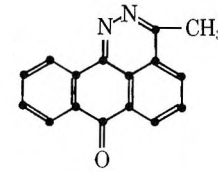


2a 11



12 13



14

tion of the dihydro form, readily reoxidized to **1b** by air. Reduction of **2b** under these conditions is not reversible, but causes degradation of the system.

Experimental Section

Melting points are corrected.

1-(Bromoacetyl)anthraquinone (1d). A solution of 11.0 g (0.043 mol) of 1-acetylanthraquinone (**1b**)[5] in 150 ml of acetic acid was stirred on the steam bath during the addition over a 1-hr period of a solution of 7.8 g (2.5 ml, 0.049 mol) of bromine in 10 ml acetic acid. The reaction mixture was heated 15 min longer and then cooled and filtered to yield 11.1–12.6 g (79–89%) of buff colored solid, mp 188° dec. Additional product was obtainable from the filtrate by dilution. Crystallization from toluene (26 ml/g) gave an 84% recovery of white needles, dec 192°.

Anal. Calcd for $C_{16}H_9O_3Br$: C, 58.4; H, 2.7; Br, 24.3. Found: C, 58.6; H, 2.7; Br, 24.1.

1-(Dibromoacetyl)anthraquinone (1g), prepared in the same way but with two equivalents of bromine, crystallized as a white solid from toluene, dec 189–191°, depressed on admixture with **1d**.

Anal. Calcd for $C_{16}H_8O_3Br_2$: C, 47.1; H, 2.0. Found: C, 46.9; H, 2.0.

1-Methoxy-2,6-aceanthrylenedione (2b). To a solution of 5.0 g (0.020 mol) of 1-acetylanthraquinone (**1b**) in 200 ml of dimethyl sulfoxide was added 23 ml of "Triton B" solution (35% benzyltrimethylammonium hydroxide in methanol), causing the color to change from pale yellow-green to purple. For 2 hr, a gentle stream of air was passed through the solution, which turned greenish. The product separated upon the addition of 35 ml of acetic acid followed by 50 ml of methanol. Chilling, filtration, and washing with methanol gave 2.1–2.6 g (40–50%) of brick red solid, mp 233–6° dec. (The attempt to isolate further material from the mother li-

quor was unsuccessful.) Crystallization from pyridine or acetic acid did not affect the mp.

Anal. Calcd for $C_{17}H_{10}O_3$: C, 77.9; H, 3.8; mol wt, 262. Found: C, 77.9; H, 3.8; mol wt (mass spectrum), 262.

Under similar conditions 1,5-diacetylanthraquinone (**12**)[5] gave 7-acetyl-1-methoxy-2,6-aceanthrylenedione (**13**), crystallizing from acetic acid as a brick red solid, dec 246–253°.

Anal. Calcd for $C_{19}H_{12}O_4$: C, 75.0; H, 3.9; mol wt, 304. Found: C, 74.9; H, 4.0; mol wt (mass spectrum), 304.

Oxidative Degradation of 2b. To a solution of 1.0 g of **2b** in 20 ml of hot acetic acid was added a solution of 1.0 g of CrO_3 in about 5 ml of 50% acetic acid. The resulting mixture was heated 10–15 min on the steam bath, cooled, diluted, and filtered to give a mixture of solids that was digested with sodium bicarbonate solution. The soluble fraction consisted of 0.16 g of pale yellow 1-anthraquinonecarboxylic acid (**1e**), which crystallized from 2-nitrobutane as an off-white solid of mp 289–293° dec, unchanged on admixture with an authentic specimen. Identification was confirmed by ir comparison. The insoluble fraction was insoluble in NaOH as well and consisted of 0.53 g of very pale yellow methyl 1-anthraquinoneglyoxylate (**1f**), mp 234–240°. Crystallization from acetic acid raised the mp to 238–243°. It showed three distinct carbonyl bands at 1680, 1712, and 1755 cm^{-1}.

Anal. Calcd from $C_{17}H_{10}O_5$: C, 69.4; H, 3.4; O, 27.2; mol wt, 294. Found: C, 69.5; H, 3.4; O, 27.4; mol wt (mass spectrum), 294.

1,2-Aceanthrylenedione (**5a**) was prepared from oxalyl chloride and anthracene by the procedure of Liebermann and Zsuffa.[3] It condensed rapidly with *o*-phenylenediamine in refluxing pyridine to give the orange quinoxaline (**7a**), which could be crystallized from chlorobenzene or pyridine, mp 245–247°.

Anal. Calcd for $C_{22}H_{12}N_2$: C, 86.8; H, 4.0; N, 9.2. Found: C, 87.1; H, 3.7; N, 9.2.

6-Bromo-1,2-aceanthrylenedione (5c). A solution of 10.4 g (0.045 mol) of 1,2-aceanthrylenedione (**5a**) in 25 ml of nitrobenzene, heated in an oil bath to 140–145°, was stirred with an efficient stirrer while a solution of 2.50 ml (7.80 g, 0.049 mol) of bromine in 10 ml of nitrobenzene was added dropwise during a period of approximately 1.5 hr. The thick mixture was heated and stirred 15 min longer, cooled, and diluted with alcohol to facilitate the filtration, which gave, after washing with a little alcohol and drying, 11.0–11.9 g (80–85%) of tan product, dec *ca.* 252–256°. Crystallization from *o*-dichlorobenzene (1.1 ml/g) gave an 85% recovery, dec 264–267°. Yellow analytical specimens, dec *ca.* 260–264°, were obtained by crystallization from pyridine, acetic anhydride, or methoxyethanol.

Anal. Calcd for $C_{16}H_7O_2Br$: C, 61.8; H, 2.3; Br, 25.7. Found: C, 62.1; H, 2.2; Br, 25.4.

Oxidation with CrO_3 in refluxing acetic acid gave a good yield of 1-anthraquinonecarboxylic acid (**1e**), identified by melting point, mixture melting point, and ir comparison. *o*-Phenylenediamine condensed rapidly with **5c** in boiling pyridine to give a quantitative yield of the quinoxaline (**7c**), which crystallized from chlorobenzene or nitromethane as a bright yellow solid, mp 289–290°.

Anal. Calcd for $C_{22}H_{11}BrN_2$: C, 69.0; H, 2.9; Br, 20.9; N, 7.3. Found: C, 69.0; H, 3.0; Br, 20.6; N, 7.3.

6-Methoxy-1,2-aceanthrylenedione (5b). A solution of sodium methoxide was prepared from 1.0 g of 57% sodium hydride by washing with petroleum ether and dissolving in 50 ml of methanol. To this was added 1.00 g (3.2 mmol) of **5c**, followed by 15–20 min stirring at reflux, cooling, dilution, and filtration to give 0.70 g (83%) of orange product, dec from 190°. Crystallization from acetic acid or toluene raised the dec temperature to about 230°.

Anal. Calcd for $C_{17}H_{10}O_3$: C, 77.9; H, 3.8; mol wt, 262. Found: C, 77.8; H, 3.8; mol wt (mass spectrum), 262.

Condensation with *o*-phenylenediamine was effected by 15-min heating in pyridine solution on the steam bath, giving the orange quinoxaline (**7b**), mp 227–229° dec. Crystallization from acetic acid or toluene raised the melting point to 229–230° dec.

Anal. Calcd for $C_{23}H_{14}N_2O$: C, 82.7; H, 4.2; N, 8.4. Found: C, 82.9; H, 4.1; N, 8.3.

6-Piperidino-1,2-aceanthrylenedione (5d). A mixture of 1.5 g (4.8 mmol) of **5c** and 1.2 ml (1.0 g, 12 mmol) of piperidine in 50 ml of ethanol was stirred at reflux for 4 hr, chilled, and filtered, yielding 1.4 g (93%) of purple-brown product, mp 196–201° dec. Crystallization from acetic acid or isobutyl alcohol raised the melting point to 202–205°.

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 80.0; H, 5.4; N, 4.5. Found: C, 79.8; H, 5.2; N, 4.2.

Quinoxaline (**7d**) was prepared from **5d** by refluxing for 0.5 hr with a slight excess of *o*-phenylenediamine in pyridine solution, followed by cooling, dilution, and filtration. The product was obtained in quantitative yield, mp 211–217°. Crystallization from methylcyclohexane containing a little toluene gave an orange solid, mp 217–220°.

Anal. Calcd for $C_{27}H_{21}N_3$: C, 83.7; H, 5.4; N, 10.9. Found: C, 83.4; H, 5.2; N, 11.1.

3-Methyldibenzo[*de,h*]cinnolone-7 (14) was prepared from **1b** and hydrazine hydrate by refluxing for 1 hr in ethanol and crystallized from methoxyethanol: mp 260–261°.

Anal. Calcd for $C_{16}H_{10}N_2O$: C, 78.0; H, 4.1; N, 11.4. Found: C, 78.4; H, 4.0; N, 11.5.

Acknowledgment. The authors are grateful to K. Valentin for nmr and mass spectra, and to J. Kobliska and his staff for microanalyses.

Registry No.—**1b,** 53336-60-0; **1d,** 53336-61-1; **1e,** 602-69-7; **1f,** 53336-62-2; **1g,** 53336-63-3; **2b,** 53336-64-4; **5a,** 6373-11-1; **5b,** 53336-65-5; **5c,** 53336-66-6; **5d,** 53336-67-7; **7a,** 203-22-5; **7b,** 53403-85-3; **7c,** 53336-68-8; **7d,** 53336-69-9; **12,** 53336-70-2; **13,** 53336-71-3; **14,** 53336-72-4; o-phenylenediamine, 95-54-5; piperidine, 110-89-4; hydrazine hydrate, 10217-52-4.

References and Notes

(1) Presented at the 168th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1974.
(2) J. Houben, "Das Anthracene und die Anthrachinone," Leipzig, 1929.
(3) C. Liebermann and M. Zsuffa, *Chem. Ber.*, **44**, 202 (1911).
(4) C. Liebermann and M. Kardos, *Chem. Ber.*, **47**, 1203 (1914).
(5) H. F. Bassilios, M. Shawky, and A. Y. Salem, *Recl. Trav. Chim. Pays-Bas*, **82**, 298 (1963).

Conformational Properties of Azacyclooctanes

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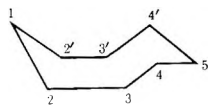
The 270-MHz ^1H spectra and the 22.6-MHz ^{13}C spectra have been obtained for azacyclooctane (azocane) and its *N*-methyl and *N*-chloro derivatives between room temperature and −120°. A coalescence is observed in each case at about −95° in the ^1H spectra. The ^{13}C spectra remain unchanged throughout the temperature range. The results are consistent with a boat–chair conformation in which the nitrogen resides at the BC(1) position on the molecular plane of symmetry. Pseudorotation is ruled out as the process responsible for the changes in the ^1H spectra because of the temperature invariance of the ^{13}C spectra. The spectral changes are therefore attributed to the slowing of boat–chair/boat–chair ring reversal. For the N–H and N–CH_3 systems, nitrogen inversion is fast at these temperatures, but for N–Cl the process should be slow on the nmr time scale.

Theory and experiment alike have gravitated to the boat–chair (1) as the favored conformation for cyclooctane



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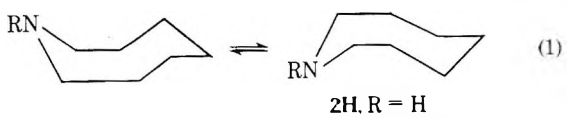
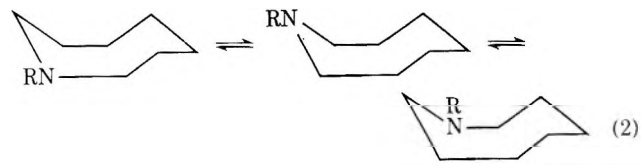
and many of its derivatives.[2,3] When one or more methylene groups in cyclooctane are replaced with a heteroatom, nonbonded and eclipsing interactions are changed considerably, so that conformational minima may differ. Nmr studies of oxygen derivatives[4] have indicated that oxocane (one oxygen) exists as a boat–chair with the oxygen in the BC(1) position, 1,3-dioxocane exists as a boat–chair with the oxygens in the BC(1) and BC(3) positions, 1,3,6-trioxocane exists as a mixture of twist–boat–chair and twist–chair–chair conformations, and 1,3,5,7-tetraoxocane exists as a mixture of twist–boat–chair and symmetrical crown conformations.

The present study was initiated to examine the conformational properties in solution of azacyclooctanes, in which one methylene group of cyclooctane has been replaced with NR. Such a change in the molecular structure raises a number of questions. (1) What conformation do azacyclooctanes assume? (2) At what position does the nitrogen atom reside? In conformations other than the symmetrical crown, there are several distinct positions, in contrast to cyclohexane. In the boat–chair (1), for example, the nitrogen has the choice of five positions. (3) Does the substituent on nitrogen assume an axial-like or an equatorial-like position? (4) What dynamic processes operate in the molecule? If there is a preference for the boat–chair, which possesses a plane of symmetry, the molecule may undergo a ring reversal process (eq 1) very similar to that of cyclohexane. By this process, an axial group is interchanged with its geminal equatorial counterpart. If the time scale of the nmr experiment is responsive to this process, then the protons in a given CH_2 group (disregarding for the time being effects of substituents on nitrogen) will change from enantiotopic to diastereotopic, as the temperature is lowered. This process does not affect the positional identity of the various atoms, as numbered in 1. Pseudorotation, on the other hand, averages ring positions as well as substituent identities. A boat–chair can be transformed into another boat–chair, probably through a twist–boat–chair intermediate, with alteration of positional identity, as in eq 2. In this



(1)

2H, R = H
2M, R = CH_3
2C, R = Cl



(2)

manner the nitrogen atom can be moved around the ring in an orderly fashion. The substituents are averaged to two noninterconverting sets: 1e, 2e, 3a, 4a, 5a, 4′a, 3′a, 2′e; and 1a, 2a, 3e, 4e, 5e, 4′e, 3′e, 2′a. Thus, geminal groups are not interchanged by pseudorotation. In cyclooctane, only when all positions are averaged by pseudorotation and when geminal groups are interchanged by ring reversal do all protons become equivalent. In azacyclooctanes, the ^{13}C spectrum can thus be of use to determine the location of the nitrogen. If it is located on the boat–chair plane of symmetry (positions 1 or 5), the ^{13}C spectrum will not change with temperature. If it is located off the plane of symmetry (positions 2, 3, or 4), changes will be observed as pseudorotation is frozen out. For example, if azacyclooctane should exist as the BC(2) form, a dynamic process would be observed (see eq 2), and at the slow-exchange limit carbons 3,3′ and 4,4′ (respectively) would become nonequivalent. The ^{13}C spectrum is not sensitive to the process of ring reversal, so that spectral changes can only derive from hindered pseudorotation. A third dynamic process, inversion about nitrogen, is also possible in azacyclooctanes. This process interconverts the axial and equatorial positions on nitrogen without involving the remainder of the ring. Only if nitrogen inversion is frozen out can the conformational preference of the substituent on nitrogen be determined. If the molecule is biased entirely toward one substituent position, then the spectrum will not be altered as nitrogen inversion is slowed.

In order to answer these questions, we have examined the ^1H spectra at 270 MHz and the ^{13}C spectra at 22.6 MHz of azacyclooctane (**2H**) and its *N*-methyl (**2M**) and *N*-chloro (**2C**) derivatives. A high-field, superconducting magnet system was necessary to differentiate proton resonances. From the temperature dependence of the ^1H spectra and the temperature independence of the ^{13}C spectra, we conclude that all these azacyclooctanes exist in the boat–chair conformation with the nitrogen at the BC(1) position. Tentative conclusions about the location of the substituents on nitrogen are reached.

Results

The 270-MHz ^1H spectrum of azocane (heptamethylenimine or azacyclooctane, **2H**) at room temperature (Figure

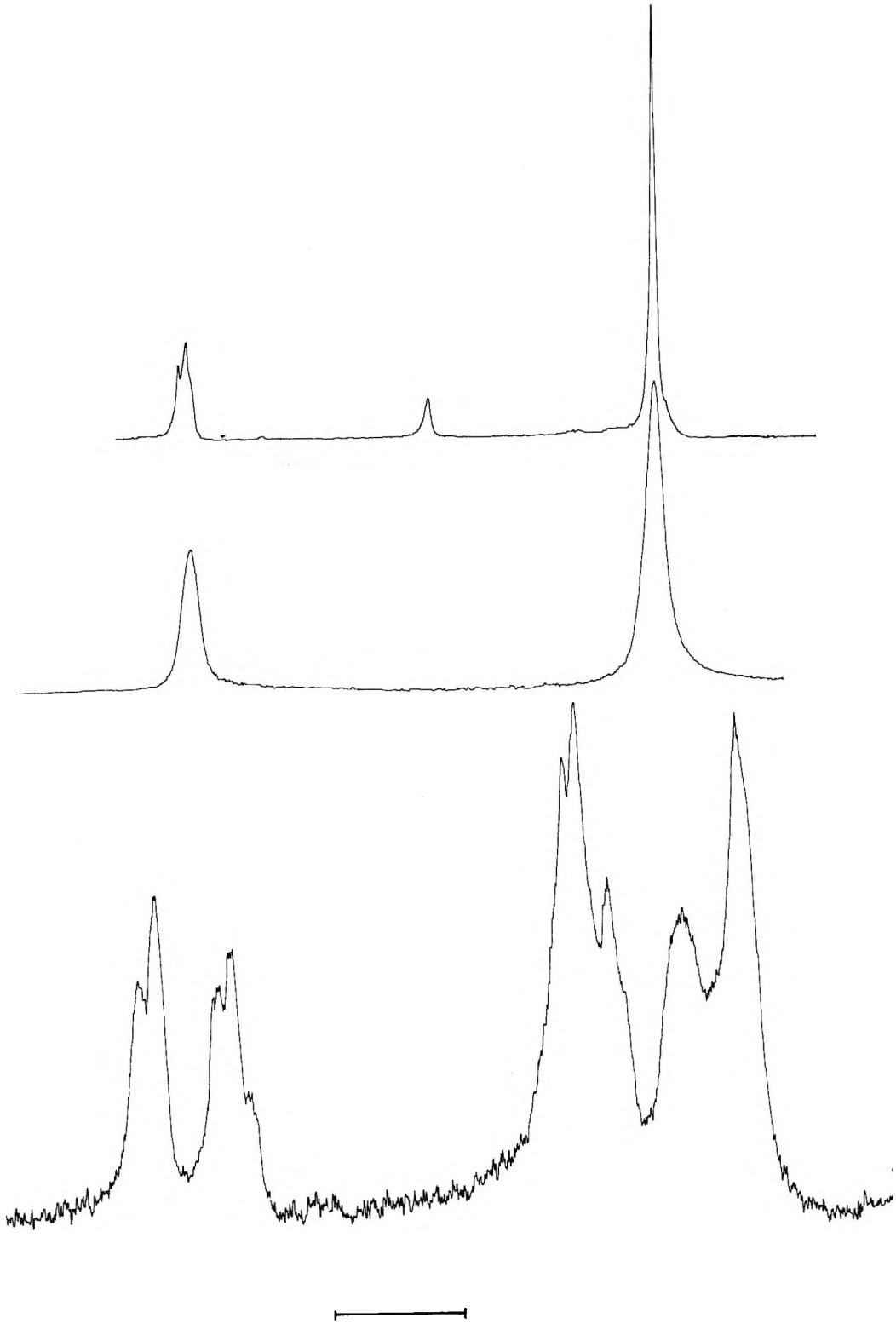


Figure 1. The 270-MHz ^{1}H spectrum of azocane (**2H**, heptamethylenimine) in $CHClF_2$ as a function of temperature (top to bottom, +19, −80, −107.5°). The room-temperature peaks occur approximately at δ 2.2, 2.8, and 3.4. The calibration bar represents 90 Hz.

1) contains a broad singlet at δ 2.2 for the ten β, γ, and δ protons. The NH proton falls at 2.8, and the α-methylene protons give a second-order triplet at 3.4. As the temperature is lowered, the resonances from the protons on carbon broaden. The resonance from the proton on nitrogen broadens, moves downfield, and ultimately disappears because of quadrupolar relaxation and a lower rate of proton exchange. At −107.5°, the α-methylene resonance has reached the slow-exchange limit as a pair of 1:1 multiplets, which form essentially an AB quartet ($\Delta\nu$ = 0.22 ppm) with additional vicinal splitting. The remaining methylene protons produce a multiplet at higher field, with at least five overlapping components, which arise from chemical-shift differences of three distinct sets of diastereotopic geminal protons (β, γ, and δ).

The room-temperature 270-MHz ^{1}H spectrum of *N*-methylheptamethylenimine (**2M**) is given in Figure 2. The methyl singlet occurs at δ 2.3, the α-methylene resonance at 2.5, and the resonances of the remaining protons at 1.6. As the temperature is lowered to −109°, the methyl and α-methylene resonances undergo only slight broadening. The resonance of the remaining methylene groups, however,

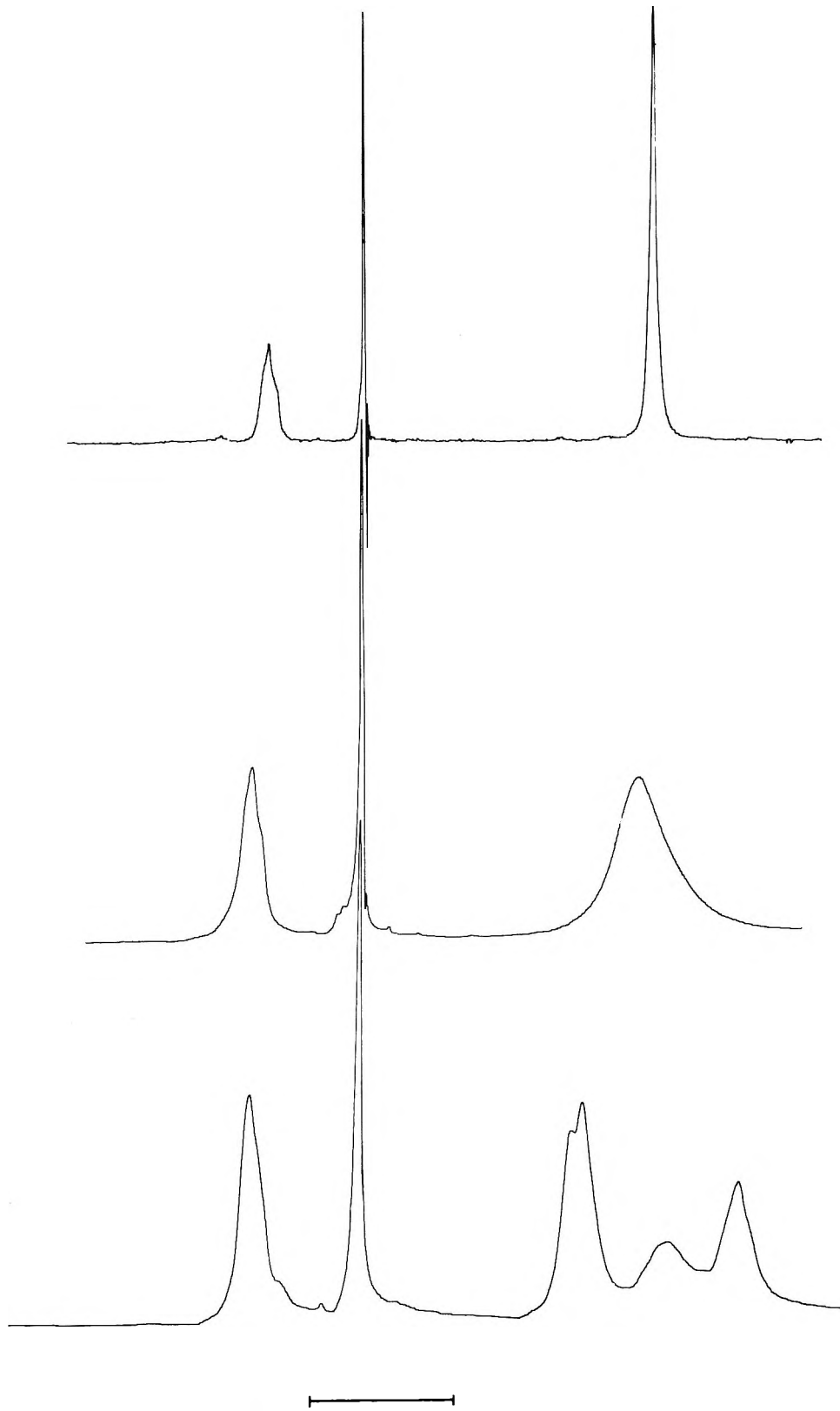


Figure 2. The 270-MHz ^1H spectrum of *N*-methylheptamethylenimine (**2M**) in $CHClF_2$ as a function of temperature (top to bottom, +19, −80, −109°). The room-temperature peaks occur approximately at δ 1.6, 2.3, and 2.5. The calibration bar represents 90 Hz.

broadens considerably at −80° and becomes a multiplet containing at least four components at the slow-exchange limit.

At room temperature, the α-methylene protons of *N*-chloroheptamethylenimine (**2C**) produce a sharp, well-resolved triplet at δ 3.2 (Figure 3). The two-peak resonance from the remaining methylene groups contrasts with the analogous singlet resonances of the NCH_3 and NH compounds. Most likely, the electron-withdrawing nature of the *N*-chloro group has pulled the resonance of the β protons to a lower field (1.9) than that of the γ and δ protons (1.6). As the temperature is decreased, all resonances broaden. The α-methylene triplet loses its fine structure at −80°, and finally becomes a doublet of unequal intensities (about 1:3) at −109°. This result contrasts with the 1:1 doublet for the NH compound and the singlet for the NCH_3 compound. The high-field peaks broaden, merge, and resolve into at least two very broad multiplets. There is

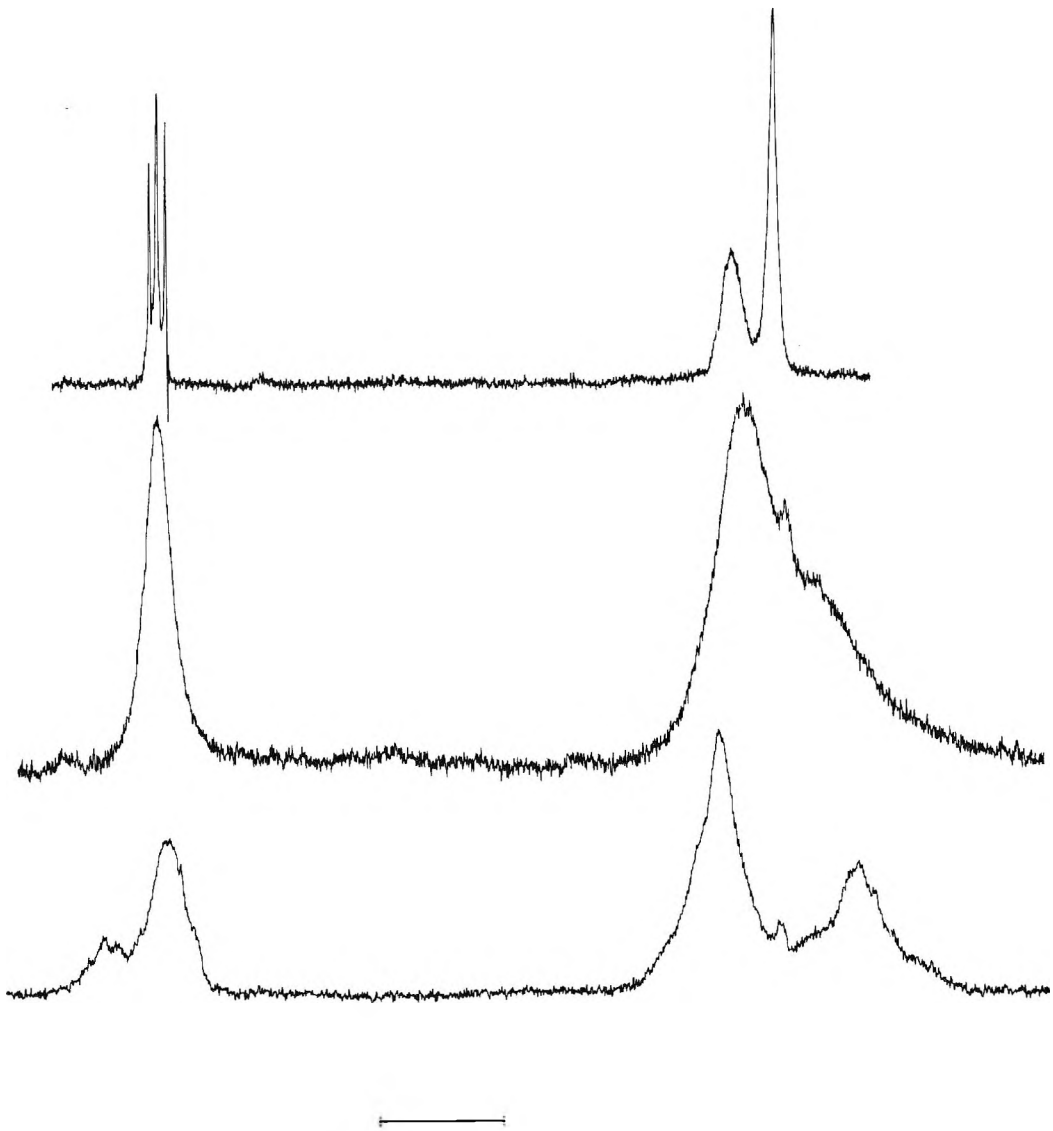


Figure 3. The 270-MHz ^{1}H spectrum of *N*-chloroheptamethylenimine (**2C**) in $CHClF_2$ as a function of temperature (top to bottom, +19, −80, −109°). The room-temperature peaks occur approximately at δ 1.6, 1.9, and 3.2. The calibration bar represents 90 Hz.

a strong similarity among the β, γ, and δ resonances for all three systems at −109°.

The ^{13}C spectra of **2H, 2M,** and **2C** were examined at 22.6 MHz between room temperature and −120° (Figure 4). The α-carbon resonances fall at lowest field. The β, γ, and δ carbons each give distinct resonances at higher field, with the δ-carbon peak recognized by its lower intensity. There was essentially no change with temperature over this 150° range in any of the spectra.

Discussion

The ^{13}C spectra of all three systems under study (**2H, 2M, 2C**) contain four resonances (ignoring the methyl peak) in the approximate ratio 2:2:2:1, and do not exhibit changes as the temperature is lowered to −120°. The ^{1}H spectra of the three compounds, on the other hand, pass through an exchange process over this same temperature range. Because a slowing of pseudorotation should have been evident in the ^{13}C spectrum, we can conclude without equivocation that the observed changes in the ^{1}H spectra are due to a slowing of ring reversal. Because only four peaks are observed in the ^{13}C spectra, the preferred conformation, assuming a boat–chair, must either possess a plane of symmetry [BC(1) or BC(5)] or undergo rapid pseudorotation to produce a plane of symmetry on the average [BC(2) ⇌ BC(2′), etc.]. The present data do not differentiate between these two possibilities. A similar quandary was reached in the oxocane study,[4] but the authors favored the BC(1) form with a static plane of symmetry. The azocane and oxocane data are essentially identical. We likewise favor the BC(1) conformation because it permits the largest amount of relief from nonbonded interactions. The remarkable similarity between the high-field multiplets in the ^{1}H slow-exchange spectra of **2H, 2M,** and **2C** points toward a common conformation. Although no attempt was made to measure accurate barriers from the changes in the ^{1}H spectra, the approximate coalescence temperatures (∼−95°) and chemical-shift differences (0.22 ppm for the α protons of **2H**) lead to barriers for boat–chair/boat–chair ring reversal of about 8–9 kcal/mol.

We do not believe that the spectral changes in any of the systems are due to nitrogen inversion. We have previously studied this process in the *N*-methyl and *N*-chloro cyclic imines of ring size four through seven.[5] It is clear from our earlier investigations that nitrogen inversion or proton exchange is very rapid in secondary imines such as **2H,** so that no spectral changes are expected in the temperature range examined in the present study. One can estimate a barrier to nitrogen inversion for the *N*-methyl system from data in other ring systems.[5] The expected result (∼6.5 kcal/mol) does not correspond to the present observations (8–9 kcal/mol). Furthermore, the *N*-methyl compound is ex-

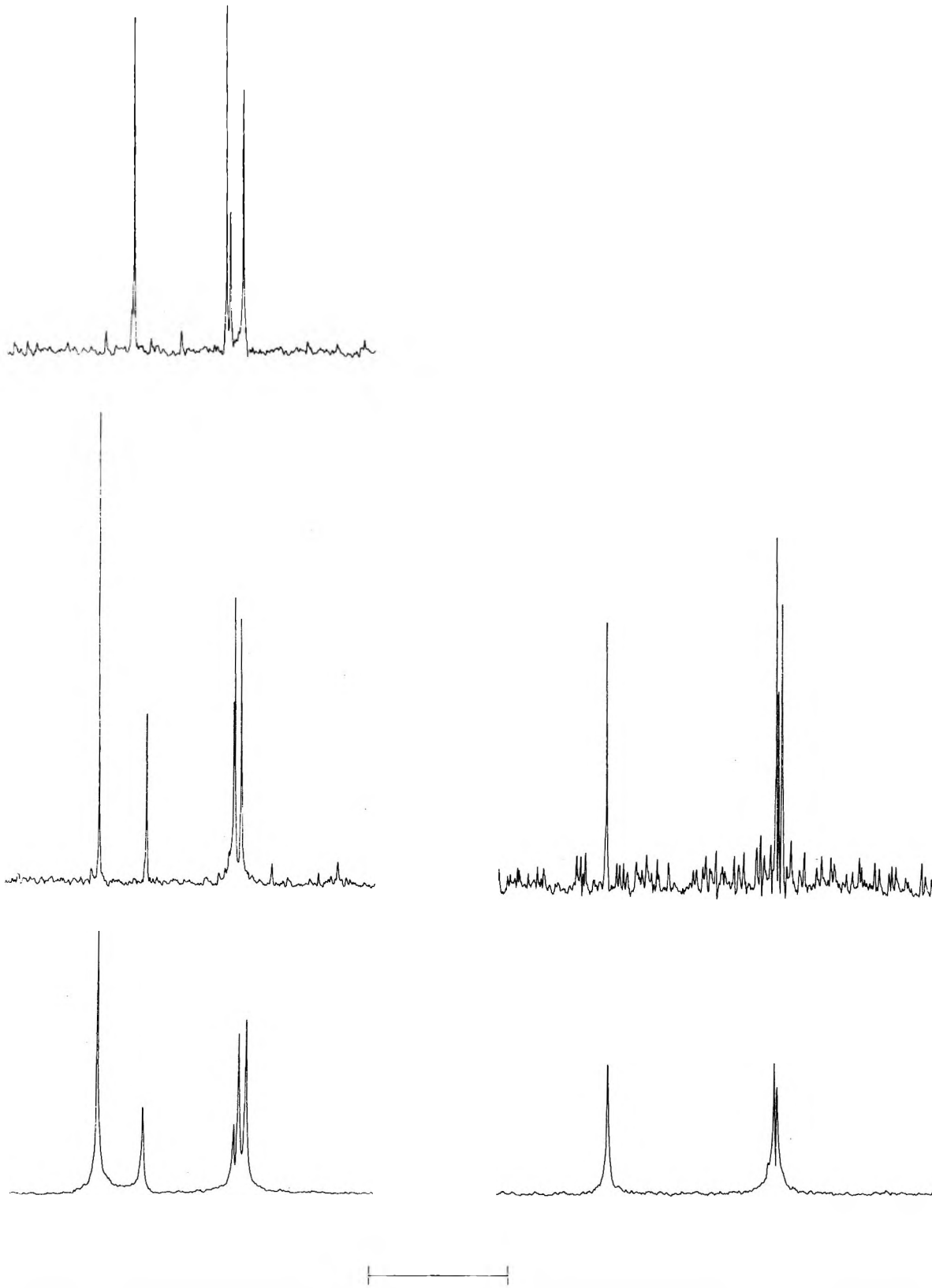


Figure 4. (Top) The 22.6-MHz ^{13}C spectrum of heptamethylenimine (**2H**) at 25°. The peaks lie at 29.0 (β or γ), 31.8 (δ), 32.6 (β or γ), and 52.0 (α) ppm below TMS. (Middle) The 22.6-MHz ^{13}C spectrum of *N*-methyl- (**2M**, left) and *N*-chloroheptamethylenimine (**2C**, right) at 25°. The peaks for **2M** lie at 30.0 (β or γ), 31.2 (β or γ), 31.5 (δ), 49.8 (CH_3), and 59.8 (α) ppm below TMS. The peaks for **2C** lie at 29.5 (β or γ), 30.3 (δ), 30.7 (β or γ), and 66.5 (α) ppm below TMS. (Bottom) The ^{13}C spectra of **2M** (left) and **2C** (right) at −120°. The calibration bar represents 30 ppm. In collection of the data, a pulse width of 80–100 μsec, a dwell time of 100 μsec, a delay time of $^1/_{16}$ μsec, and a total sweep width of 5000 Hz were used. Each spectrum is the average of 512 transients.

pected to exist as a biased equilibrium. The axial BC(1) form should be much less favored than the equatorial form, since the 1–3 interactions are even greater than in cyclohexane.[6] Thus, even if nitrogen inversion becomes slow on the nmr time scale, the spectrum of **2M** will not be altered. The situation is much the same as that in *N*-methylpiperidine, which exhibits hindered ring reversal[7] but gives no evidence for hindered nitrogen inversion even though the barrier is not excessively low, since the equilibrium lies well on the side of the equatorial form.[8]

The α-proton resonance of **2H** is a well-spaced AB quartet (Figure 1). The axial proton at the 2 position of a boat–chair is shielded to a greater extent by the 1–2′ and 3–4 bonds than is the 2-equatorial proton, just as in cyclohexane. The 1-equatorial position in the boat–chair is nearly eclipsed with the 2-equatorial position, so that introduction of a 1-methyl group will strongly shield the 2-equatorial proton but have little effect on the 2-axial proton. As can be seen from Figure 2, the α-equatorial proton resonance of **2M** has indeed moved upfield to a point of superposition with the axial proton resonance. This frequency lies very close to that of the high-field (2-axial) resonance in **2H.**

The asymmetry of the α-proton resonance of the *N*-chloro derivative **2C** is puzzling. Below −100°, inversion about nitrogen bearing a chlorine substituent should be slow.[5] Therefore, if both the axial and equatorial chlorine conformations are populated, separate ^1H and ^{13}C resonances should be observable. One possible explanation of the spectral asymmetry of the α-proton resonance thus is the presence of two conformers. This explanation is unlikely, however, because of the insensitivity to temperature of the ^{13}C spectrum over a range that should have revealed multiple conformations, if present. We are not able to provide an explanation for the asymmetry of the α-proton resonance in the spectrum of the *N*-chloro compound without invoking a second conformation that for some reason is not manifested in the ^{13}C spectrum.

To summarize these studies, we have found that the ^1H and ^{13}C spectra of azocane (azacyclooctane, heptamethylenimine) and of its *N*-methyl and *N*-chloro derivatives are consistent with the boat–chair conformation, in which the nitrogen atom is at the BC(1) position on the plane of symmetry. As in the case of oxocane,[4] other explanations are not excluded. Changes in the ^1H nmr spectrum below −80° and the lack thereof in the ^{13}C spectrum indicate that the process of boat–chair/boat–chair ring reversal becomes slow on the nmr time scale, and possesses a barrier of about 8–9 kcal/mol. There is no evidence for a slowing of pseudorotation over this temperature range. Inversion about nitrogen in the NH and NCH_3 molecules appears to be nmr fast, although in the latter case the point is moot because a biased equilibrium prevails, with the methyl group entirely equatorial. The configuration of chlorine is not determined with certainty.

Experimental Section

Infrared spectra were measured on a Beckman IR-5 spectrophotometer. Preliminary and routine nmr spectra were recorded on Varian Associates T-60 or Hitachi Perkin-Elmer R20B spectrometers operating at 60 MHz. All ^1H spectra reported in this paper were obtained at 270 MHz on the Bruker HX-270 equipped with a variable temperature probe.[9] The ^{13}C spectra were obtained on a Bruker HFX-10 spectrometer operating at 22.6 MHz and equipped with a variable-temperature probe, broad-band decoupler, Nicolet Model 1074 computer for data acquisition, and Digital Corp. Model PDP8/L computer with Teletype I/O for Fourier transformation. The ^{13}C spectra were obtained as the free induction decay with broad-band ^1H decoupling and converted to the frequency domain by Fourier transformation. Further details are given in the caption of Figure 4. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. 60076.

Heptamethylenimine (2H, azocane, azacyclooctane) was obtained from Aldrich Chemical Co. and used without further purification. *Anal.* Calcd for $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.52; H, 13.43; N, 12.32.

***N*-Methylheptamethylenimine (2M).** A solution of formic acid (2.12 ml, 56 mmol, Allied Chemical Co.) and heptamethylenimine (2 g, 18 mmol) was cooled in running tap water. This mixture was added to a 36% formaldehyde solution (1.92 g, 23 mmol, J. T. Baker) and heated to 95–100°. When CO_2 began to evolve, the flask was removed from the heating bath. After the evolution of CO_2 had ceased, the mixture was heated again for 7 hr at 95–100°. To the cooled mixture was added 8 ml of 2 *N* HCl, and the water was removed by distillation *in vacuo*. The syrupy yellow residue was dissolved in 8 ml of distilled water. To this solution, 8 ml of saturated aqueous KOH was added to effect separation of the imine. The product was extracted with ether (3 × 20 ml), and the ether solution was filtered, washed with brine, dried ($MgSO_4$), and filtered, and the ether evaporated. The colorless product was purified by distillation: bp 144–146° (760 mm); yield 45%.[10] *Anal.* Calcd for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.00. Found: C, 75.70; H, 13.55; N, 10.98.

***N*-Chloroheptamethylenimine (2C).** Heptamethylenimine (2 g, 18 mmol) in 50 ml of dry ether was carefully added to *N*-chlorosuccinimide (3.85 g, 29 mmol, Aldrich Chemical Co.) in 40 ml of dry ether. The mixture was stirred for 1.5 hr and then washed with distilled water and 5 *N* HCl. The ether layer was filtered, washed with brine, dried ($MgSO_4$), and filtered, and the ether evaporated. The colorless product was purified by bulb-to-bulb distillation: yield 58%.[10] *Anal.* Calcd for $C_7H_{14}NCl$: C, 56.94; H, 9.55; N, 9.48. Found: C, 56.70; H, 9.50; N, 9.40.

Registry No.—**2H,** 1121-92-2; **2M,** 19719-81-4; **2C,** 37546-26-2.

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A Kinetic Study of the Reaction between Sulfite Ion and Propylene Oxide[1a]

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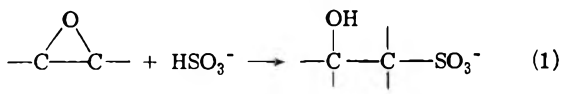
The reactive sulfur species in the sulfur(IV)–propylene oxide reaction is sulfite ion. The reaction is first order in sulfite and also first order in propylene oxide under conditions of dilute base in nearly pure water. The reaction order with respect to propylene oxide becomes less than one as the propylene oxide concentration is increased. These observations are consistent with simple nucleophilic attack by the sulfite ion, and with strongly concentration-dependent activity coefficients for propylene oxide.

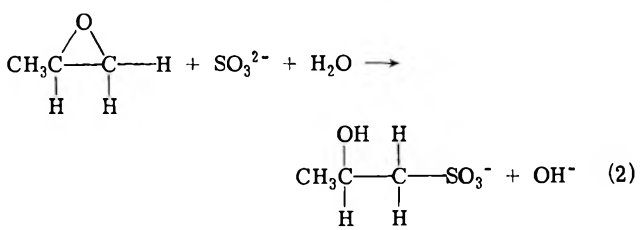
Reactions between epoxides and sulfur(IV) generally result in ring opening[2] as illustrated by eq 1. If the ring carbon atoms in the reactant are substituted unsymmetrically, then nonequivalent sites for sulfur(IV) attack exist and either or both of the isomeric products may be obtained.[2] If one of the ring carbon atoms is bound to more bulky substituents than the other, as in propylene oxide, then the major product is usually predicted to have the sulfonate group in the terminal position owing to smaller steric resistance to attack at the terminal carbon atom.[2] However, this generalization is not valid for every reaction. For example, the reactions of sulfite with styrene oxide and with 1,2-epoxyoctane have been reported to give only the corresponding 2-sulfonic acids.[3] The product of the sulfite reaction with propylene oxide, the epoxide of principal interest in the present report, has been reported to give only the terminal sulfonate[4,5] but may give a mixture.[6] Even greater disagreement exists about the product of the sulfur(IV)–epichlorohydrin reaction. A product with a normal terminal sulfonate group has been reported,[7] but the reaction has also been reported[8] to give under some conditions terminal sulfonate by replacement of the chloride, without disturbing the ring. However, this last report has been questioned.[9]



(1)

Some very early observations of epoxide reactions with sulfite were made,[10] but not much work has been done recently.[9] One moderately recent study[3] was a stoichiometric and kinetic investigation of the reaction between sulfite and styrene oxide in two phases. It was concluded that sulfite ion is the reactive sulfur(IV) species and that the reactions are first order in sulfite ion; however, an attempt to study the reaction between propylene oxide and sulfite in a single aqueous phase was not successful because the reaction was too fast to study by methods then available.

Owing to our interest in reactions of sulfur(IV)[11] and to the absence of detailed kinetic data for reactions of the class shown in eq 1, we have studied the sulfur(IV)–propylene oxide reaction indicated by eq 2 and have made a few observations of some related reactions.



(2)

Experimental Section

Reagents. Oxygen-free aqueous sodium sulfite solutions and sodium perchlorate solutions were prepared as described earlier.[12] Reagent grade sodium carbonate, sodium hydroxide, perchloric acid, ethylene oxide, propylene oxide, propylene sulfide, epichlorohydrin, epibromohydrin, and deuterium oxide were used without purification. The water used for preparation of each solution was redistilled from laboratory distilled water and was stored in a polyethylene tank.

Rate and Nmr Measurements. Rates of reaction 2 were measured at 4.0, 14.1, and 25.0° in aqueous alkaline solutions of 0.25 *M* ionic strength maintained with $NaClO_4$. The reactant solutions were contained in 5- or 10-cm spectrophotometer cells positioned in a Beckman ACTA V recording spectrophotometer. The progress of each reaction was observed by measuring the absorbance decrease at 270 nm, where SO_3^{2-} is the principal absorbing species. Propylene oxide was in large excess in each experiment. Each individual experiment was first order in sulfite and the pseudo-first-order rate constant was obtained from a plot of ln $(A - A_\infty)$, *vs.* time, where A and A_∞ are the absorbances at 270 nm at a particular time and at completion of the reaction, respectively.

The procedures used in the propylene oxide experiments were also used in attempts to measure the rate of reaction of sulfite ion with ethylene oxide and with propylene sulfide. These same procedures were also used in attempts to measure the rates of reaction with epichlorohydrin and epibromohydrin, except the solvent was 50% ethanol owing to the insolubility of these organic compounds in pure water.

A Varian XL-100 spectrometer was used to measure the proton nmr spectra of the reactants and products of reaction 2 and of the analogous epichlorohydrin reaction in D_2O solution.

Results

Reaction Product. We used proton nmr spectra to confirm that the sulfonate group in the reaction 2 product is indeed in the terminal position as expected[2] and as asserted by some earlier workers.[4,5] Our measurement of the spectrum of reactant propylene oxide gave an upfield doublet assigned to the methyl group. In addition to the upfield doublet, multiplets centered at 75 and 93 MHz downfield from the doublet and a poorly resolved multiplet centered at 108 MHz downfield from the doublet were observed. The spectrum had the same appearance as spectra reported earlier[3,14] for propylene oxide. In addition, our assignments are in agreement with the earlier ones;[13,14] the methyl group resonance is upfield, the resonances for the two hydrogen atoms on the other terminal carbon atom are at 75 and 93 MHz, and the resonance for the remaining hydrogen atom is at 108 MHz downfield.

Reaction 2 was allowed to occur in D_2O solution under conditions of excess sulfite so that all the propylene oxide was converted to product. The proton nmr spectrum of the resulting solution had the following downfield resonances (still referred to the upfield doublet for propylene oxide): a doublet centered at 8 MHz assigned to the methyl group, multiplets at 113 and 120 MHz assigned to the hydrogen atoms on the terminal carbon atom containing the sulfonate group, and a multiplet at 190 MHz assigned to the hydrogen atom on the central carbon atom. The assignment of the downfield multiplet is based on the low relative intensity and on the similarity in shape to the analogous mul-

Table I
Observed Pseudo-First-Order Rate Constants for Reaction 2 at 0.25 *M* Ionic Strength and 0.005–0.01 *M* NaOH

$[C_3H_6O]$,[a] mol %	$10^3k'$, sec^{-1}	$[C_3H_6O]$,[a] mol %	$10^3k'$, sec^{-1}
0.534	0.208[b]	0.192	0.218[c]
1.08	0.447	0.485	1.49
2.23	1.24	0.980	2.54
3.20	1.44	1.03	2.62
3.44	1.58	2.02	5.64
3.70	1.78	2.06[d]	5.83
4.74	1.35	2.06[e]	5.73
6.12	0.940	2.06[d,f]	5.77
7.58	0.759	4.28	9.90
7.89	0.645	5.75	12.6
0.520	0.510	9.78	15.4
1.05	0.672	17.1	14.2
2.16	2.31	27.3	12.6
4.61	3.08	36.8	11.1
5.95	3.22	41.1	10.6
7.37	2.25		

[a] Mole per cent solvent, considering only propylene oxide and water. [b] Each of the first ten rate constants listed in this column was measured at 4.0°. The remaining six were measured at 14.1°. [c] Each of the rate constants listed in this column was measured at 25.0°. [d] $[OH^-]$ was 0.0094 *M*. [e] $[OH^-]$ was 0.00504 *M*. [f] The reaction occurred in an oxygen-free solution.

Table II
Observed and Calculated Values for k^0 and Activation Parameters for k^0, Valid in the Limit as [PO] Approaches Zero

Rate constant k^0[a] 4°	14.1°	25°	ΔS^*, eu	ΔH^*, kcal/mol
0.045	0.108	0.290	2.5	14.0

[a] The rate constants are defined by eq 4; the units are (mole fraction)$^{-1}$ sec^{-1}.

tiplet in propylene oxide. We conclude that the hydroxyl group in the reaction 2 product is indeed on the central carbon atom, rather than on the terminal one, because the resonance assigned to this hydrogen atom shifted farther downfield than any of the other peaks, in accord with the greater deshielding strength of OH relative to SO_3^- or SO_3H.

We were able to measure an nmr spectrum of epichlorohydrin that agrees with spectra already reported,[15] but the products of the reaction of epichlorohydrin with excess sulfite in D_2O solution apparently include at least two organic species. The nmr spectrum of the product mixture is complex and is not consistent with complete conversion to any one of the three expected products (1-chloro-2-hydroxy-3-sulfonic acid,[7] 1-chloro-3-hydroxy-2-sulfonic acid, or 1,2-epoxy-3-sulfonic acid[8]).

Phase Properties of the Water–Propylene Oxide System. The salt-free water–propylene oxide system is known[16] to form two liquid phases at mole fractions of propylene oxide ranging from about 0.17 to about 0.90. The two-phase region exists at all temperatures between the freezing and boiling points of the liquid. The solids that can exist in equilibrium with the liquid phases are pure propylene oxide, pure water, and a clathrate compound propylene oxide · 17 water.[17] Our visual observations of the system show that addition of 0.25 *M* $NaClO_4$ renders the solvents completely miscible at 25°, but two liquid phases remain at temperatures below about 20°.

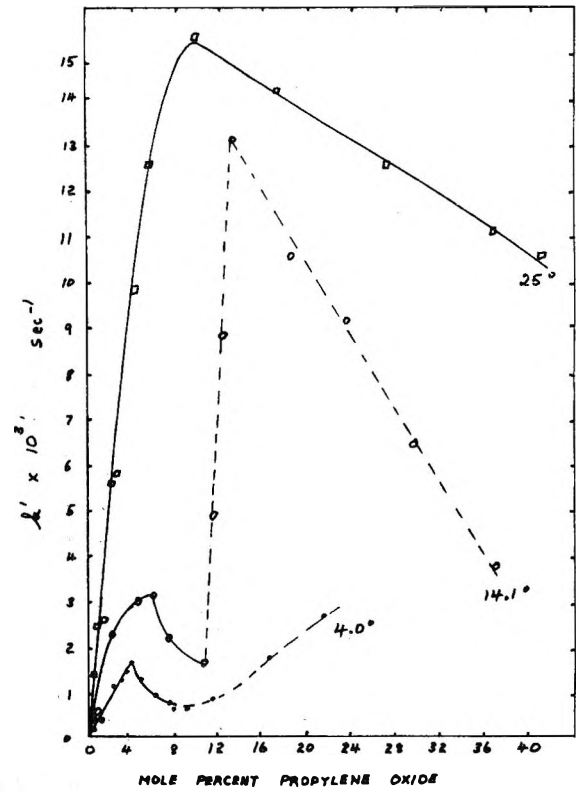


Figure 1. The relationship between observed rate constant for reaction 2, and mole per cent propylene oxide. The dashed lines connect points measured under two-phase conditions.

Rate Measurements. The numerical values of the pseudo-first-order rate constants measured for reaction 2 are listed in Table I. Each of the rate constants listed in the table occurred in a one-phase system and is defined by eq 3. These same rate constants are shown graphically in Figure 1, along with some apparent rate constants obtained from two-phase systems.

$$-\mathrm{d} \ln [SO_3^{2-}]/\mathrm{d}t = k' \quad (3)$$

Experimental results listed in Table I show that small variations in $[OH^-]$ do not affect the value of k', although experiments in dilute acid solution showed an induction period; reaction was slow until the solution became basic due to production of OH^- by reaction 2. Similarly, Table I indicates that deoxygenation of the reaction mixture does not affect the value of k'. However, solvent phase separation does affect the apparent rate constant, as indicated in Figure 1.

Even the data obtained at 25°, all in a one-phase system, indicate a complex relation between the pseudo-first-order rate constant and the mole per cent[18] propylene oxide at high mole per cent propylene oxide. However, the data obtained at each of the temperatures conform to a first-order dependence on propylene oxide at low [PO].[19] The limiting slopes obtained from Figure 1 lead to the observed rate constants given in Table II, where the rate constant k^0 is defined according to eq 4. The values of k^0 are correlated

$$-\mathrm{d} \ln [SO_3^{2-}]/\mathrm{d}t = k^0[\mathrm{PO}] \quad (4)$$

very well by the absolute rate theory equation, leading to the activiation enthalpy and entropy values of 14.0 kcal/mol and 2.5 eu, respectively, for k^0.

Some attempts were made to measure the rates of sulfite ion reaction with substrates other than propylene oxide.

Table III
Observed Pseudo-First-Order Rate Constants for Reaction of Sulfite Ion with Ethylene Oxide at 0° in Alkaline Aqueous Solution

$[C_2H_4O]$, M	$10^3k'$, sec^{-1}
0.091	1.5
0.112	2.3
0.120	2.4
0.188	1.4
0.221	3.9
0.225	3.5
0.296	5.3

The sulfite reaction with propylene sulfide was rapid and yielded a polymeric solid that did not dissolve in any of the polar or nonpolar solvents we tested. Neither epichlorohydrin nor epibromohydrin was sufficiently soluble in water to permit rate measurements in water solution. In addition, both these substrates reacted quite rapidly with sulfite. However, a rate constant was measured for epichlorohydrin at 4° in 50 vol % water–ethanol solution; the rate was first order in sulfite, and based on the assumption that the rate is also first order in epichlorohydrin, the rate constant was about 0.02 M^{-1} sec^{-1} in a solution initially containing 4.88 $\times 10^{-3}$ M epichlorohydrin, 0.01 M NaOH, and about 2.30 $\times 10^{-3}$ M SO_3^{2-}.

The reaction between sulfite ion and ethylene oxide was also quite fast and study of the reaction was further complicated by the inconvenient volatility of ethylene oxide. The ethylene oxide was added to the spectrophotometer cell by bubbling the gas into the water solution in the cell. The ethylene oxide concentration after completion of the reaction was determined by measuring the absorbance at 260 nm, using $\epsilon = 1.09$. The initial portions of the reactions had already occurred by the time rate measurements were started, and the data were only moderately reproducible. The data are listed in Table III, where k' is defined by eq 3. The k' data are approximately in accord with eq 5, where $k = 0.02\ M^{-1}\ sec^{-1}$.

$$k' = k[C_2H_4O] \quad (5)$$

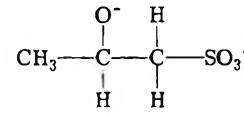
Discussion

The data at low [PO] are consistent with empirical eq 4. A possible minor contributor to the deviation from eq 4 at higher [PO] is a dependence on the activity of water; the activity of water would be expected to remain approximately constant with small changes in [PO] in nearly pure water, but would be expected to decrease slightly as [PO] becomes larger.[16] A probable major contributor to the deviation is the decreasing activity coefficient for propylene oxide with increasing [PO]. Activity coefficients for propylene oxide and water in the salt-free mixed solvent system have been determined at the normal boiling points of the system,[16] but have not been determined at any of the temperatures employed in the present study. The activity coefficient for propylene oxide at the mixed solvent boiling temperatures does decrease sharply in the [PO] range 0–0.4, however, and it appears reasonable to assume similar behavior at lower temperatures in the presence of dissolved salts. We think it is probable that either eq 6 or 7 accurately represents the rate behavior for reaction 2 in the one-phase reaction mixtures containing up to 0.41 mol fraction propylene oxide. The first-order dependence on sulfite ion concentration and the negligible importance of terms involving bisulfite concentration are well established by our work. Our conclusion that sulfite is the reactive sulfur(IV) species is in agreement with the conclusion reached from the earlier study,[3] although the earlier study did involve heterogeneous systems and the investigators apparently did not realize that SO_3^{2-} and HSO_3^- are in equilibrium in aqueous solutions.

$$-\mathrm{d}\ \ln [SO_3^{2-}]/st = ka_{PO}a_{H_2O} \quad (6)$$

$$-\mathrm{d}\ \ln [SO_3^{2-}]/\mathrm{d}t = ka_{PO} \quad (7)$$

The form of eq 4 is consistent with simple attack of the nucleophile sulfite ion upon the terminal ring carbon atom of propylene oxide to give



as the product of the rate-determining step if eq 7 is correct, or to give the final net reaction product if eq 6 is correct.

With respect to the reactions we studied more briefly than reaction 2, our results with ethylene oxide are not inconsistent with a mechanism analogous to that described just above for propylene oxide. The stoichiometric evidence for the epichlorohydrin reaction permits no generalization except that at least two competing pathways exist for reaction with sulfite. The sulfite-induced polymerization of propylene sulfide is not surprising; if the initial reaction is analogous to reaction 2, then a mercaptan is formed and the mercaptan could act as a nucleophile in attacking another propylene sulfide molecule to give a sulfur bridged dimer containing another mercaptan group capable of continuing the polymerization. A detailed description of an analogous process for the ethoxide-induced polymerization of propylene sulfide has already been presented.[20]

Registry No.—HSO_3^-, 15181-46-1; propylene oxide, 75-56-9; ethylene oxide, 75-21-8.

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Notes

Specific Solvation Effects on Acylation of Amines in Solvents with Low Dielectric Constants

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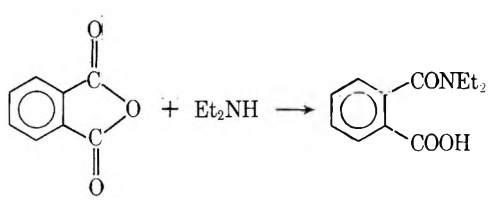
Kinetic solvent effects in solvents of relatively low dielectric constants are generally treated in a nonspecific manner. Differences in rate are usually reconciled using either an electrostatic approach[1] or the regular solution theory.[2] Certain solvents in this category, *e.g.*, chloroform and ether, in spite of similar dielectric constant and solubility parameter, may, however, exert tremendously different, and sometimes opposite, kinetic solvent effects because of their different ability to either accept or donate electrons to the reactants and/or transition state. In these cases, the kinetic solvent effects have to be viewed through specific solute–solvent interactions. In this communication, we present kinetic data of the aminolysis of phthalic anhydride in solvents of relatively low dielectric constants, *viz.*, cyclohexane, chloroform, diethyl ether and tetrahydrofuran (THF). It is shown that the apparent reaction rate and mechanism in these solvents are vastly different. The effect of added acid on the apparent aminolysis rate is shown to be dramatically solvent dependent, being catalytic in some solvents and inhibitory in others. Opposing solvent kinetic effects were also observed when acylation rates of phthalic anhydride by diethylamine and morpholine in mixed chloroform–cyclohexane solvents were compared. In the reaction with diethylamine, the rate increased with the chloroform content of the solvent, whereas the opposite was observed for the acylation reaction with morpholine. The collective data, however, can be interpreted in terms of a generalized reaction scheme which takes into account the role of each individual solvent on the reaction steps.

Results and Discussion

The stoichiometry of the reactions between phthalic anhydride and diethylamine (Et_2NH) in all the solvents studied is as given in eq 1.



(1)

In all the solvent systems studied, it was impossible to use one single rate expression to describe the entire course of the reaction. Therefore, initial and terminal rate expressions were separately determined. Initial rate plots as a function of diethylamine concentration are presented in Figure 1, and it can be observed, in the amine concentrations studied, that the reaction rate was about 10–120 times faster in chloroform and tetrahydrofuran than in ether and cyclohexane. It is also evident that even among the initial rates measured, the rate dependence on amine concentration was influenced by solvent. The apparent rate expressions are presented in Table I.

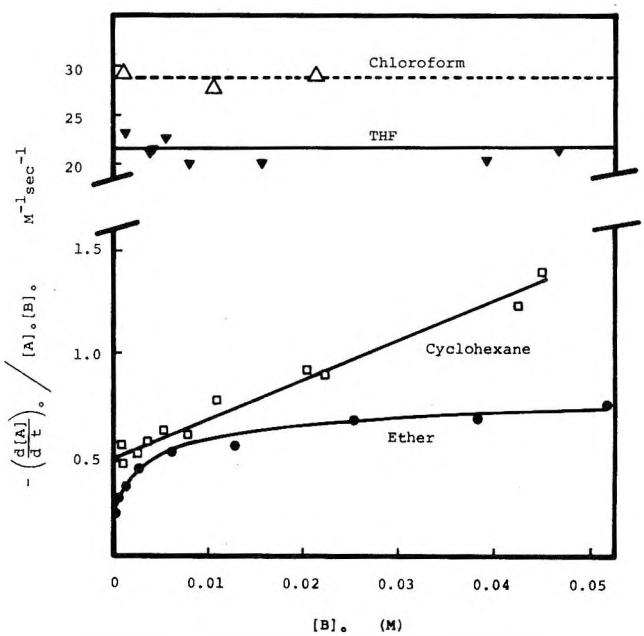


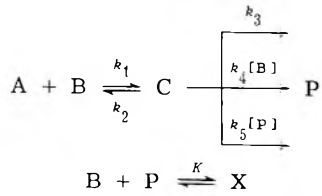
Figure 1. Initial rate plots of $-(d[A]/dt)_0/[A]_0[B]_0$ *vs.* $[B]_0$ for the reaction between phthalic anhydride and diethylamine in chloroform (△), tetrahydrofuran (▼), cyclohexane (□), and diethyl ether (●) at 25°.

The terminal rate expressions are even more complex than the initial rates because of the participation of the reaction product, *N,N*-diethylphthalamic acid, in the reaction. For example, in chloroform, the terminal rate was found to be slower than the initial rate, whereas in tetrahydrofuran, the reverse was true (Table I). It was also found that in any particular solvent, added acetic acid affected the acylation rate in a manner similar to that of added phthalamic acid, whereas added acetamide had no effect. Apparently, the carboxylic acid group, rather than the amide function, in the reaction product caused the effects on the observed rate changes.

In the presence of excess acetic acid the rate of disappearance of phthalic anhydride was first order in each solvent. The kinetic effects of added acetic acid on the ratio of observed pseudo-first-order rate constant over $[B]_0$ are shown in Figure 2. It appears that acetic acid catalyzed the reaction in both ether and THF. In ether, at the higher concentration of acetic acid, catalysis appeared to level off. In cyclohexane, the reaction between phthalic anhydride and diethylamine was accelerated at low acetic acid concentrations but inhibited at high acetic acid concentrations. In chloroform, the overall effect was inhibition. No simple relationship between the observed rate and acetic acid concentration could be formulated in ether and cyclohexane. Empirical rate expressions could be written for the reaction occurring in chloroform and THF; these are presented in Table I.

Scheme I depicts a series of reactions which can account for the kinetic results obtained for the acylation of diethylamine by phthalic anhydride in all the solvents studied.

Scheme I



In this scheme A is the anhydride, B the dialkylamine, and P the phthalamic acid. C is the reactive intermediate which can decompose to re-form the reactants (reaction 2) or to yield the phthalamic acid either in a spontaneous reaction (reaction 3), in a reaction catalyzed by a molecule of the dialkylamine (reaction 4), or in a reaction catalyzed by a molecule of the phthalamic acid (reaction 5). X is an unreactive complex formed by association of a molecule of amine with one or more phthalamic acid molecules. If a carboxylic acid is added to the reaction system, it is believed to participate in reactions similar to those of the phthalamic acid, since catalysis by the amide function appeared to be negligible.

In the absence of any evidence for an accumulation of C during the course of the acylation, the rate laws which describe Scheme I can be developed by using a steady-state approximation. Thus, in the absence of any added acid and when $[B]_0 \gg [A]_0$ and $[P]_0 = 0$, the initial rate of disappearance of anhydride is given by

$$-\left(\frac{d[A]}{dt}\right)_0 = \frac{k_1(k_3 + k_4[B]_0)}{k_2 + k_3 + k_4[B]_0}[A]_0[B]_0 \qquad (2)$$

The observed initial rate expressions in the solvents studied (Table I) can all be derived from eq 2. The differences arise because the relative magnitudes of the rate constants differ in the solvents. Thus, in Scheme I, it can be assumed that $k_3 \ll k_4[B]_0$ in ether, $(k_2 + k_3) \gg k_4[B]_0$ in cyclohexane, and $k_3 \gg k_4[B]_0$ in chloroform and THF.

From Scheme I, the rate of disappearance of anhydride when $[P] \neq 0$ is given by

$$\frac{-d[A]}{dt} = \frac{k_1 f(k_3 + fk_4[B]_0 + k_5[P])}{k_2 + k_3 + fk_4[B]_0 + k_5[P]}[A]_0[B]_0 \qquad (3)$$

where

$$f = (1 + K[P])^{-1} \qquad (4)$$

Again, the observed data in all solvents for the terminal rates or in those cases when acid is added can be derived from eq 3; the solvent plays its role in determining again the relative magnitudes of the rate constants as well as the contribution of the inhibiting equilibrium to the overall scheme. Thus, in ether and THF, the catalytic effects noted in the presence of small concentrations of P or of added acid (which appears in equivalent terms to those of P) would be expected when $K[P] \ll 1$ and $k_5[P]$ as well as $(k_3 + k_4[B]_0)$ was smaller than or comparable in size to k_2.

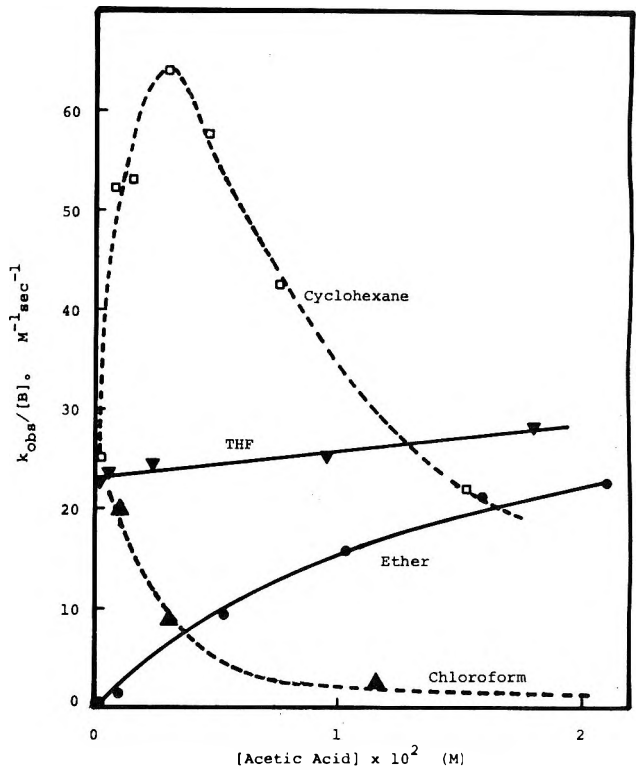


Figure 2. Effects of added acetic acid on $k_{obsd}/[B]_0$ of reaction between phthalic anhydride and diethylamine in chloroform (▲), tetrahydrofuran (▼), cyclohexane (□), and diethyl ether (●) at 25°. $[A]_0 \approx 1.3 \times 10^{-4}$ *M* in all solvents.

Since the complexation constant between acetic acid and diethylamine in ether is low ($K \simeq 50\ M^{-1}$),[3] the assumption of $K[P] \ll 1$ is valid at low [P]. The same situation will hold in the case of THF in which the complexation constant is expected to be even lower. When [P] or acetic acid concentration is high, the inhibitory effect will begin to become significant, and the catalytic contribution of [P] or added acid will be diminished (Figure 2). In cyclohexane, when high [P] is present, the overall effect is that of inhibition because the equilibrium constant, *K*, is much larger.[4] In chloroform, the term $k_5[P]$ is presumably small and no catalysis is observed, even at very low acid concentrations.

The formation of nonreactive complexes can also be invoked in viewing the solvent effects when the acylation rates of phthalic anhydride by diethylamine and morpholine in mixed chloroform–cyclohexane solvents were compared (Figure 3). In the reaction involving diethylamine, acylation was catalyzed by chloroform. However, in the acylation of phthalic anhydride by morpholine, an opposite solvent effect was observed in that the reaction was drastically inhibited in the presence of chloroform. We have determined that morpholine forms both 1:1 and 1:2 complexes with chloroform, with equilibrium constants at 25°

Table I
Summary of Observed Rate Expressions for Both Initial and "Terminal" Rates for Reaction between Phthalic Anhydride (A) and Diethylamine (B) in Various Solvents at 25°[a]

Solvent	Initial rate expression	"Terminal" rate expression
Cyclohexane	$0.49[A]_0[B]_0 + 18.7[A]_0[B]_0^2$	See text
Ether	$565[A]_0[B]_0^2/(1 + 1.02 \times 10^3[B]_0)$	See text
Chloroform	$28.2[A]_0[B]_0$	$25[A]_0[B]_0/(1 + 1000[P])$
THF	$21.2[A]_0[B]_0$	$22.8[A]_0[B]_0 + 280[A]_0[P][B]_0$

[a] [P] = [acetic acid]. Concentrations are in molar units and time is in seconds.

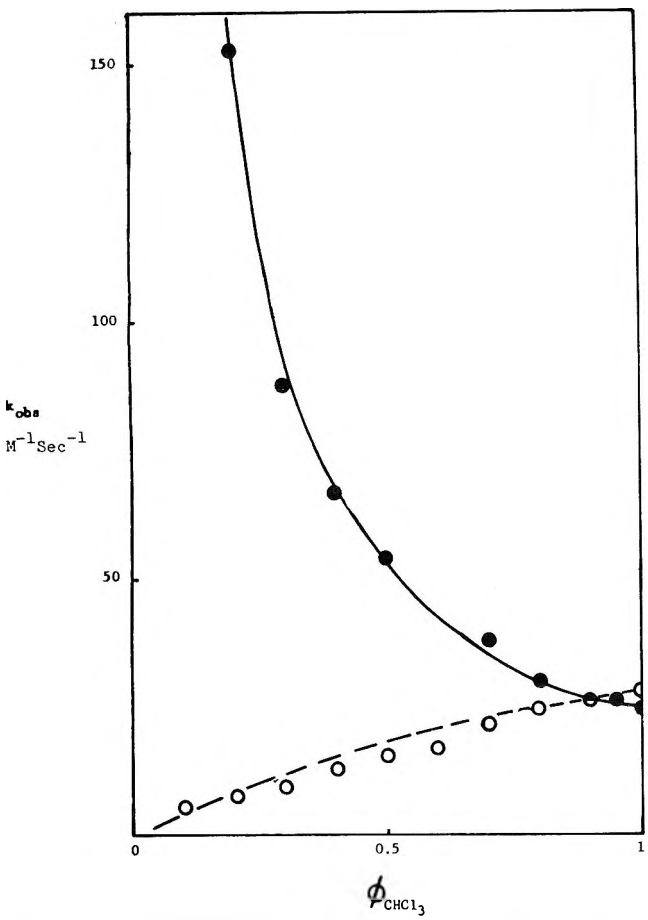


Figure 3. Initial observed rate constants *vs.* volume fraction (ϕ) of chloroform for the acylation of phthalic anhydride by morpholine (●) and diethylamine (○) in mixed chloroform–cyclohexane solvent systems.

of 1.05 M^{-1} and 0.29 M^{-2}, respectively. The stability constant for complexation between an aliphatic amine such as diethylamine with chloroform is likely to have a value of about 0.2 M^{-1} at 25°.[5] In the presence of excess chloroform relative to the amine concentration, as in the present case, the activity of morpholine may be drastically lowered through complexation without compensatory solvation of the transition state. Thus, the reaction rate is reduced with increasing content of chloroform in the reaction medium. In the case of the reaction involving diethylamine, the comparatively weaker solvation of the amine reactant by chloroform may be adequately counterbalanced by solvation of the transition state involved. Thus, inhibition by chloroform is not observed.

Experimental Section

Reagents. Unless otherwise specified, all reagents were of reagent grade. Diethyl ether (ACS) was dried over $LiAlH_4$ and distilled. Chloroform (AR) was washed with distilled water five to six times, dried over $CaCl_2$ overnight, then distilled over phosphorus pentoxide, and used immediately. Cyclohexane (AR) was distilled over phosphorus pentoxide. Tetrahydrofuran (AR) was dried by $LiAlH_4$ and distilled. All purified solvents were stored over molecular sieve (Linde 4A). Morpholine was refluxed with KOH pellets for 1 hr, fractionally distilled, and then again fractionally distilled over sodium. Diethylamine was refluxed with KOH pellets for 1 hr and then distilled. The middle fractions were collected and stored over KOH pellets. Piperidine was fractionally distilled over KOH pellets under nitrogen. The amines were stored under nitrogen in closed containers in a refrigerator. Their purity was checked by titration with standard acid. Phthalic anhydride was recrystallized from a chloroform–cyclohexane mixture; mp 129–130° (lit. mp 131.5°). *N,N*-Diethylphthalamic acid was prepared according to Maxim;[6] mp 151–152° (lit. mp 153°). Glacial acetic acid was used without purification.

Kinetic Procedure. Rates and rate constants for the acylation reactions were calculated from changes in ultraviolet absorbance at a wavelength where phthalic anhydride was the main absorbing species. Measurements were made using Cary 14, Cary 16, and Durrum stop-flow spectrophotometers. In the cases when the reactions were first order or pseudo first order (in the presence of excess amine), rate constants were calcualted from plots of log ($A - A_\infty$) against time. Initial rates were calculated from the spe of the ae to an absorbance against time plot at a point as close to zero time as possible. In these studies an accurate amount (0.01–0.1 ml) of a concentrated solution of the amine in the solvent to be studied was placed in a 1 cm absorption cell. Three milliliters of phthalic anhydride solution in the same solvent was injected into the cell through a hypodermic syringe. The instrument recorder was turned on after insertion of the needle through the cell compartment cover but before injection of the anhydride solution. For the studies of effects of acetic acid on the reaction, the proper amount of acetic acid was added to the amine before mixing with anhydride. The uv spectra of the products of the reaction, when different acids were used as catalysts, were identical. All kinetic studies were done at 25°.

Acknowledgment. This work was supported in part by Basic Research in Life Sciences, Department of the Army and a Kansas Research Grant.

Registry No.—Phthalic anhydride, 85-44-9; diethylamine, 109-89-7; cyclohexane, 110-82-7; diethyl ether, 60-29-7; chloroform, 67-66-3; THF, 109-99-9; morpholine, 110-91-8; *N,N*-diethylphthalamide, 53336-79-1; succinic acid, 110-15-6; benzoic acid, 65-85-0; trifluoroacetic acid, 76-05-1; acetic acid, 64-19-7.

Supplementary Material Available. Fuller kinetic details 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 $5.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-378.

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Solvolysis Problems in Chlorinations in Sulfuric Acid

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Recently several papers have reported chlorinations in 50–96% sulfuric acid. Kollonitsch and coworkers used Cl_2 to chlorinate α-amino acids in 100% H_2SO_4[1] and 50% H_2SO_4,[2] amines in 100% H_2SO_4,[3] and carboxylic acids in H_2SO_4–HF.[3] Minisci and coworkers published a number of papers on chlorination of esters, amines, and 1-chloroalkanes using *N*-chloro- and *N*-bromoammonium ions in 85–96% H_2SO_4.[4] Our own group has studied Cl_2 and R_2NHCl^+ chlorinations of carboxylic acids in 85–96%

Table I
Half-Lives for Solvolyses[a] of the Seven Isomeric Chlorooctanoic Acids in 84, 90, and 96% H_2SO_4 at 25°

Registry no.	Position of Cl	Half-life (hr) at 84% H_2SO_4	90% H_2SO_4	96% H_2SO_4
53431-81-5	2	$>10^3$	$>10^3$	$>10^3$
53431-82-6	3	$>10^3$	$>10^3$	$>10^3$
53431-83-7	4		2×10^2	4×10
53466-52-7	5	2×10^2	11	1.5
53431-84-8	6	70	5.2	1.0
53431-85-9	7	50	5.5	0.9
1795-62-6	8	$>10^3$	$>10^3$	$>10^3$

[a] The inertness of the 2-Cl and 8-Cl acids was demonstrated by nmr monitoring. Using these as standards, disappearance rates were determined by periodic dilution of aliquots with ice, ether extraction of the acids, esterification with diazomethane, and gc of the methyl esters as described in ref 6 and 13.

H_2SO_4,[5-8] ethers[6-8] in 85–96% H_2SO_4, alcohols in 20–70% H_2SO_4,[6-9] and alkanes in 84% H_2SO_4.[10]

A potential hazard in these chlorinations is that the chloro substitutent will selectively solvolyze and the product ratios be altered. This paper describes some experiments on the solvolysis of chlorooctanoic acids which show that the solvolysis of chloro substituents is highly sensitive to the H_2SO_4 concentration and to the position of the secondary chloro substituent relative to the carboxyl function.

The rates of solvolysis increase from 84 to 96% H_2SO_4 (Table I). This acid catalysis can be rationalized in terms of acidic species (H_3O^+, H_2SO_4) pulling off chloride ion. The value of $-\mathrm{d} \log k/\mathrm{d}H_R'$ is ~1.4 for the 5-, 6-, and 7-chlorooctanoic acids.[11]

The solvolysis rates also increase with an increase in distance between chloro substituent and carboxyl group up to the 6-chloro (rates for 6-Cl and 7-Cl are equal). This is a result of the positive charge that develops on the carbon undergoing substitution. The carboxyl group inhibits the formation of this positive charge and protonation of the carboxyl[12] intensifies this effect.

We regret to state that these results invalidate the conclusion that chlorination of octanoic acid by Cl_2 in 96% H_2SO_4 gives selectivity for 4-Cl and 8-Cl products.[13] The apparent selectivity was in fact the result of selective destruction of the 5–7 chloro products.

This same problem affects (to a lesser extent) other chlorination studies. Most of Minisci's chlorinations were conducted in 96% H_2SO_4. Selective solvolysis must have been significant in products derived from reactants such as methyl hexanoate and heptanoate so that the selectivity for $\omega - 1$ chlorination is greater than the 70–80% reported. In our own work, octanoic acid was reported to give 80% 7-chlorooctanoic acid in 84% H_2SO_4.[6] At 84% H_2SO_4, the ratio of $RCOOH_2^+$ to RCOOH is about 4 so that higher selectivity for $\omega - 1$ chlorination would be expected in 96% H_2SO_4 where protonation of octanoic acid is more complete. However, this was not found and the selectivity for $\omega - 1$ seemed to be much less. It is now clear that the selectivity was probably greater, but that this was obscured by selective solvolysis. The results of Kollonitsch were on such short chains[1-3] that selective solvolysis would be unlikely. However, extrapolation of Kollonitsch's conclusions and methods to longer chains would excounter selective solvolysis problems.

Registry No.—H_2SO_4, 7664-93-9.

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Improved Procedures for Ethynylcarbinol Hydration and Oxime Reduction to Amino Alcohols[1]

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Because of a need for 3-amino-2-methyl-2-butanol (**1**) and 1-(1-aminoethyl)cyclohexanol (**2**) in other research, we considered several routes for their synthesis. Early syntheses of **1** involved catalytic reduction of the oxime of 3-hydroxy-3-methyl-2-butanone[3] and of 2-methyl-3-nitro-2-butanol[4] over Raney nickel, whereas **2** has been prepared in several steps starting from cyclohexanone cyanohydrin.[5-7] As either the yields or the procedures involved in the earlier syntheses left much to be desired, we have developed improved procedures for **1** and **2**. The chemistry used should be readily adaptable to the preparation of other amino alcohols.

The starting materials were the readily available ethynylcarbinols, $R_2C(OH)C{\equiv}CH$, **3a** and **3b**, prepared by reaction of acetone and of cyclohexanone, respectively, with acetylene.[8] Although reference to the hydration of aceylenes to ketones is frequently made,[9] the best yield for the preparation of 1-acetylcyclohexanol by this method that we have located in the literature is 69% in a two-step reaction of ethynylcyclohexanol with mercuric oxide and sulfuric acid.[10] We have obtained a 90% yield by a simplified one-step process. Similarly, 3-hydroxy-3-methyl-2-butanone was obtained from **3a** in 80% yield.

The ketones were then converted into the corresponding oximes which were hydrogenated over 5% rhodium-on-alumina[11] to yield the desired **1** and **2** in excellent overall yield. This facile high-yield reduction of hydroxy oximes over a rhodium catalyst is notable in view of our unsuccessful attempts to reduce the same oximes catalytically over platinum or palladium catalysts. In addition, reduction procedures involving sodium in liquid ammonia or $LiAlH_4$ in ether failed to yield the desired amino alcohols in more than small yield.

Monoacylation of **1** and **2** on nitrogen was effected in over 90% yields by carrying out the acylation with 1 equiv

of acetic anhydride in absolute ethanol. The effectiveness of this method of monoacetylation[12] should be noted.

Experimental Section

3-Hydroxy-3-methyl-2-butanone. To a warm vigorously stirred solution of 65 g of yellow mercuric oxide in 500 ml of water and 90 ml of concentrated sulfuric acid was added dropwise 420.5 g (5.0 mol) of 2-methyl-3-butyn-2-ol[8] during 1.5 hr. The mixture was then heated to 70° for 30 min, cooled, and filtered through a Celite layer. The organic product was extracted into ether and the ether layer washed with water and $NaHCO_3$ solution. After pouring through a layer of $MgSO_4$ the solvent was removed and the residue distilled to yield 409.5 (80%) of 3-hydroxy-3-methyl-2-butanone, bp 137.8–139.0° (750 mm).

1-Acetylcyclohexanol. In a similar way 620 g of 1-ethynylcyclohexanol[8] was converted into 640 g (90%) of 1-acetylcyclohexanol, bp 100–101° (25 mm).

3-Hydroxy-3-methyl-2-butanone Oxime. To a well-stirred solution of 102.1 g (1.0 mol) of 3-hydroxy-3-methyl-2-butanone, 112 g of hydroxylamine hydrochloride, 400 ml of ethanol, and 50 ml of water was added portionwise 80 g of NaOH pellets. After heating to reflux for 10 min after the NaOH had all dissolved the reaction mixture was cooled and diluted with 500 ml of water, and the product isolated by ether extraction. On distillation 90 g (84%) of the oxime, mp 86–87°, was obtained.

1-Acetylcyclohexanol Oxime. In a manner similar to the above 142 g of 1-acetylcyclohexanol was converted into the oxime which was isolated by crystallization from benzene instead of distillation. The product, mp 104–105°, was obtained in 90% yield.

3-Amino-2-methyl-2-butanol (1). A solution of 23.4 g (0.2 mol) of 3-hydroxy-3-methyl-2-butanone oxime in 125 ml of freshly distilled absolute ethanol was shaken with 1.25 g of 5% rhodium-on-alumina[12] at about 40 psi for 9.5 hr. After removal of the catalyst by filtration through Celite, there was obtained 19.0 g (94%) of **1**, bp 59–61° (2 mm), as a colorless oil. The vacuum should be broken through a KOH tower in order to prevent access of CO_2 which produces a colorless solid immediately on contact with **1**. For acetylation 10.3 g (0.1 mol) of the freshly distilled amine was dissolved in 75 ml of ethanol and treated dropwise with 10.2 g (0.1 mol) of acetic anhydride. After refluxing the mixture for 30 min the alcohol was removed under reduced pressure. Vacuum distillation afforded a white solid which was recrystallized from benzene–hexane to yield 13.3 g (92%) of 3-acetylamino-2-methyl-2-butanol, mp 83.5–84.5°. This compound proved identical with that prepared previously by Liang[13] by the hydrolysis of 4,5,5-trimethyloxazolidone to **1** followed by acetylation essentially as above.

Anal.[14] Calcd for $C_7H_{15}NO_2$: C, 57.9; H, 10.4. Found: C, 58.1; H, 10.3.

1-(1-Aminoethyl)cyclohexanol (2). A solution of 31.4 g (0.19 mol) of 1-acetylcyclohexanol oxime in 150 ml of freshly distilled ethanol was reduced for 48 hr at 60–65° over 5% rhodium-on-alumina at 40–50 psi. The reaction mixture was worked up as for **1** to yield 25.7 g (90%) of **2**, bp 150–153° (40 mm), sensitive to CO_2. For acetylation 21.5 g (0.14 mol) of **2** in 100 ml of ethanol was treated with 15.4 g (0.15 mol) of acetic anhydride as in the case of **1**. After isolation as above there was obtained the acetylamino compound which distilled at 138–140° (4.5 mm). The solid distillate was recrystallized from acetone–benzene to yield 24.6 g (90%) of 1-(1-acetylaminoethyl)cyclohexanol: mp 107–108°; nmr ($CDCl_3$) δ 1.14 (d, 3 H, $CHCH_3$), 1.50 (m, 10 H, cyclohexyl protons), 1.99 (s, 3 H, $COCH_3$), 3.27 (s, 1 H, OH), 4.00 (m, 1 H, $CHCH_3$), and 6.70 (m, 1 H, NH); ir (KBr) 3.00 (NH and OH) and 6.10 μ (>C=O).

Anal.[14] Calcd for $C_{10}H_{19}NO_2$: C, 65.0; H, 10.2; N, 7.6. Found: C, 64.9; H, 10.4; N, 7.5.

Registry No.—**1**, 6291-17-4; **2**, 3183-55-9; **3a**, 115-19-5; **3b**, 78-27-3; 3-hydroxy-3-methyl-2-butanone, 115-22-0; 1-acetylcyclohexanol, 1123-27-9; 3-hydroxy-3-methyl-2-butanone oxime, 7431-25-6; hydroxylamine hydrochloride, 5470-11-1; 1-acetylcyclohexanol oxime, 53336-53-1; 3-acetylamino-2-methyl-2-butanol, 53336-55-3; 1-(1-acetylaminoethyl)cyclohexanol, 53336-54-2.

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Lithium Aluminum Hydride Reduction of 9b-(4-Chlorophenyl)-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one in Tetrahydrofuran

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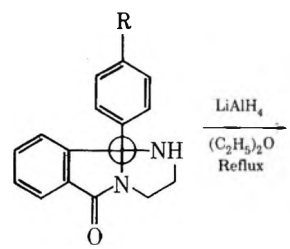
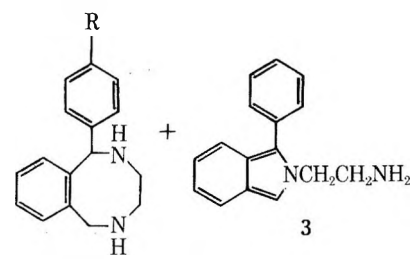
The lithium aluminum hydride ($LiAlH_4$) reduction of the 9b-aryl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones (**1a** and **1b**) in refluxing diethyl ether has been reported to give the 1-aryl-1,2,3,4,5,6-hexahydro-2,5-benzodiazocines (**2a** and **2b**)[1-4] and 2-(2-aminoethyl)-1-phenylisoindole (**3**)[3].



1a, R = H
b, R = Cl



3

2a, R = H
b, R = Cl

We have carried out the $LiAlH_4$ reduction of **1** in tetrahydrofuran (THF) at 20–25° and found that the reaction leads to different products. In the present report, our findings with 9-(*p*-chlorophenyl)-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one (**1b**) are given.[5]

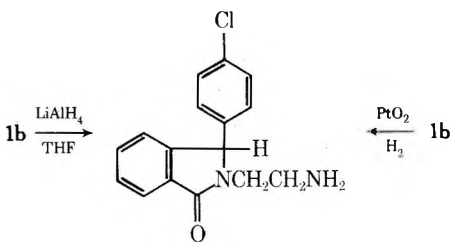
Compound **1b** was treated with $LiAlH_4$ in THF at 20–25° and then hydrolyzed with aqueous sodium hydroxide. After standing for about 4 hr at room temperature, the mixture was dried with anhydrous Na_2SO_4 to give a compound with ir and nmr spectrum in agreement with the phthalimidine (**4**). The same phthalimidine was obtained when **1b** was hydrogenated in the presence of platinum.

When the reduction was carried out as above and treated immediately after hydrolysis with anhydrous Na_2SO_4, a labile solid compound A, isomeric with **4**, was isolated in 95% yield.

Table I
^{13}C-Nmr Chemical Shifts

Compd[a]									
1b		5		9		10		11	
Ppm	C-Atom[b,c]	Ppm	C-Atom[c]	Ppm	C-Atom[c]	Ppm	C-Atom[d]	Ppm	C-Atom[d]
21.5	5	48.4	9a*	49.3	1′	53.0		51.7	1′
45.3	9a	49.5	5a*	49.9	1	64.0 to	2′,3′,4′	64.5 to	2′,3′,4′
53.4	1′	51.0	11	63.2	2,6	65.0	5′,6′	65.0	5′,6′
59.3	4′	59.5	4′		2′,6′*	94.6	1	107.9	2
60.0	8	60.4	8	60.9	4	127.7	5	136.8	5
60.4	5a	63.6	2′,6′*	64.7	3,5	138.1	4	147.9	4
63.2	7	64.3	7		3′,5′*	154.1	NCH_3	154.0	NCH_3
64.1	2′,6′*	65.1	3′,5′*	65.4	4′				
64.6	3′,5′*	68.8	6*	116.1	C-α				
68.8	6*	69.7	9*	148.5	$N(CH_3)_2$				
69.1	9*	98.1	9b						
103.0	9b	98.8	5						
141.8	3	139.5	3						
150.6	2	144.6	2						

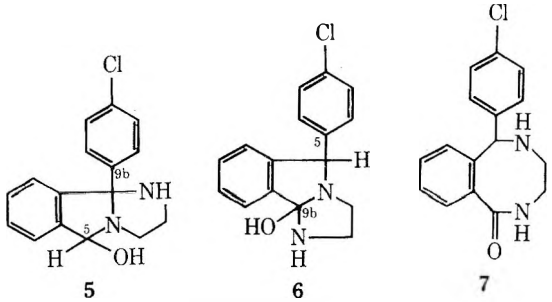
[a] The solvent was DMSO-d_6/$CHCl_3$. See ref 11 for experimental procedure. [b] The assignment of those C atoms marked with an asterisk (*) is uncertain. [c] The ^{13}C nmr of toluene and chlorobenzene were used as references to assist in these assignments. [d] The ^{13}C nmr of tetrahydrofuran and *N*-methylpyrrolidine were used as references to assist in these assignments.



4

The ir spectrum of A gave an NH or OH band at 3.10 μ and no absorption in the carbonyl region. The nmr spectrum in DMSO-d_6 gave two sets of 2 H multiplets between δ 2.6 and 3.2, a broad singlet at 3.40, a 2 H quartet[6] centered at 5.60, and 8 aromatic protons. On treatment with D_2O, the 1 H singlet at δ 3.40 exchanged and the 2 H quartet at 5.60 collapsed to a 1 H singlet at 5.62.

To account for the above data, we considered A to have either structure **5** or **6**. Compound **5** is obtained by direct

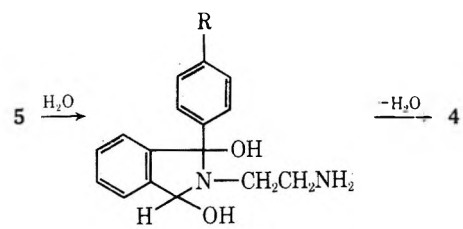


5 6 7

reduction of the carbonyl group in **1b**, whereas **6** is a tautomeric form of 6-*p*-chlorophenyl-3,4,5,6-tetrahydro-2,5-benzodiazocin-1(2*H*)-one (**7**), an intermediate proposed[4] in the diethyl ether–$LiAlH_4$ reduction of **1b** to **2b**.

When A was dissolved in THF–H_2O (9:1), a solvent system approximating that which gave **4**, and maintained at room temperature for *ca.* 20 hr, it was transformed into **4**. The rearrangement of **5** (compound A) to **4** has previously been reported by Sulkowski.[7]

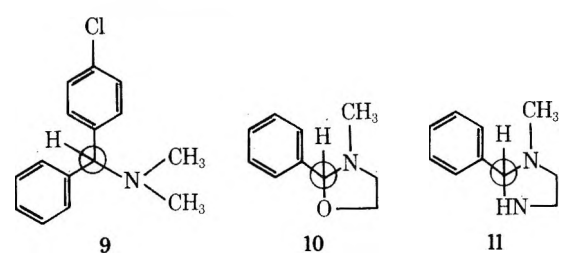
The formation of **4** may proceed by a hydration–dehydration pathway *via* the dihydroxyisoindoline (**8a**). The same type of intermediate (**8b**) has been proposed by Metlesics[8] to account for the formation of the dechloro analog of **4** from *o*-benzoylbenzaldehyde and ethylenediamine in aqueous alcohol.



8a, R = Cl
b, R = H

Structure **5** is more consistent with the nmr spectrum, whereas the formation of **4** from A in THF–H_2O is better explained by structure **6**. To distinguish between these structures, we turned to a ^{13}C nmr investigation. The two most significant C atoms for study in these compounds, C-5 and C-9b, are in such dissimilar environments that comparison of A with relevant model compounds should distinguish the structures. The model compounds selected for comparison with A were **1b**, **9**, **10**, and **11**.

The ^{13}C nmr of A gave the C-5 and C-9b carbon atom signals at 98.1 and 98.8 ppm upfield from CS_2. The relevant ^{13}C signals (circled atoms) in the model compounds were found at 103 ppm in **1b**, 116.1 ppm in **9**, 94.6 ppm in **10**, and 107.9 ppm in **11**.



9 10 11

Comparison of these values with A clearly establishes **5** as the correct structure.[9,10] The 94.6-ppm C atom in **10** is in an environment similar to C-5 in **5** and can be related with the 98.1-ppm signal in A. The 103-ppm C atom signal in **1b** is in an environment similar to C-9b in **5** and can be related with the 98.8-ppm signal in A. The 116.1-ppm C atom in **9** and the 107.9-ppm C atom in **11** are related to C-5 and C-9b, respectively, in **6** and are sufficiently different from the signals in A to eliminate **6** as a possible structure.

Experimental Section[11]

Lithium Aluminum Hydride Reduction of 9b-*p*-Chlorophenyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one (1b). A stirred mixture of 1.68 g (0.044 mol) of $LiAlH_4$ and 100 ml of dry THF, maintained under N_2, was cooled to an internal temperature of 15° and treated dropwise (10 min) with a solution of 10.0 g (0.035 mol) of **1b** in 75 ml of THF while maintaining the temperature at 20–25°. Approximately 5 min after addition was complete, the mixture was cooled to an internal temperature of 10° and treated dropwise in turn with 2 ml of H_2O, 5 ml of 15% NaOH, and 5 ml of H_2O while maintaining the temperature below 15°. The resultant mixture was allowed to stand for *ca.* 4 hr at room temperature and then treated with 10 g of anhydrous Na_2SO_4 and filtered. The salts were washed with 25 ml of anhydrous THF and the combined filtrate was concentrated *in vacuo* at a water bath temperature of 35°. The resultant solid was stirred in anhydrous diethyl ether and filtered to give 8.1 g (80%) of 2-(2-aminoethyl)-3-(*p*-chlorophenyl)phthalimidine (**4**): mp 83–85° (Et_2O–hexane); ir (KBr) 2.95 (NH_2), 5.87 μ (C=O); uv (95% EtOH) maxima 225 mμ (ϵ 23,800), 253 (3000) and 279 (1700); nmr ($CDCl_3$) δ 1.20 (2 H, NH_2, D_2O exchangeable), 3.7 (H_A), 2.6–3.1 (H_B + $2H_C$, ABC_2 m, $HCH_AH_BCH_CH_CNH_2$), 5.52 (1 H, s, ArCHAr) 6.85–7.95 (8 H, m, aromatic H).

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.0; H, 5.3; Cl, 12.4; N, 9.8. Found: C, 67.1; H, 5.3; Cl, 12.3; N, 9.8.

The reduction was repeated as above through the hydrolysis stage. The resultant mixture was treated immediately after hydrolysis with 10 g of anhydrous $MgSO_4$. The mixture was stirred for *ca.* 5 min, and then filtered. The salts were washed with 25 ml of anhydrous THF and the combined filtrate was concentrated *in vacuo* at a water bath temperature of 35° to give 9.6 g (95%) of 9b-*p*-chlorophenyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (**5**): mp 133–135° (lit.[7] mp 144–146° dec or 135°); ir (KBr) 3.05–3.10 μ (NH, OH); nmr (DMSO-d_6) δ 2.6–3.2 (4 H, 2 sets of multiplets, NCH_2CH_2N), 3.40 (1 H, broad s, D_2O exchangeable, NH), 5.60 (2 H, q, 1 H, D_2O exchangeable, OH, C^9H), 6.80–8.05 (8 H, C_6H_4, 4-ClC_6H_4); uv (95% EtOH) maxima 224 mμ (ϵ 19,400), 249 (3000), and 281 (1850); ^{13}C nmr in Table I.

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.0; H, 5.3; Cl, 12.4; N, 9.8. Found: C, 67.1; H, 5.2; Cl, 12.3; N, 9.7.

Hydrogenation of 1b. A mixture of 14.2 g (0.05 mol) of **1b**, 0.30 g of platinum oxide, and 150 ml of glacial acetic acid was placed in a Parr hydrogenation bottle and then attached to a Parr hydrogenation apparatus. The bottle was evacuated and then filled with hydrogen to a total pressure of 50 psi. After 3.0-hr agitation at room temperature, the hydrogen uptake (1 equiv of H_2) ceased. The catalyst was filtered off and the filtrate concentrated *in vacuo*. The residue was treated with 2 *N* NaOH until the aqueous phase had pH 9. It was then extracted with chloroform, dried with anhydrous $MgSO_4$, filtered, and concentrated to give 12.2 g (85%) of **4**, mp 84–85°. This substance gave ir and nmr spectrum identical with 4 prepared by $LiAlH_4$ reduction of **1b**.

Conversion of 5 to 4. A solution of 1.0 g of **5** in 25 ml of THF–H_2O (9:1) was stirred for *ca.* 20 hr at room temperature. The tlc analysis ($CHCl_3$–CH_3OH, 9:1) revealed that **5** had been converted into a new substance. The solvent was removed *in vacuo* to give 0.91 g of a substance that gave ir and ^1H nmr and mp (83–85°) identical with **4** obtained in the $LiAlH_4$ reduction of **1b**.

1-(*p*-Chlorophenyl)-1-phenyl-*N,N*-dimethylmethylamine (9). A solution of 10.4 g (0.05 mol) of 4-chlorbenzhydrol, 30 ml of thionyl chloride and 150 ml of dry chloroform was stirred and refluxed until gas evolution (HCl, SO_2) had ceased. The solvent was removed *in vacuo* and the crystalline residue dissolved in 150 ml of dry tetrahydrofuran, cooled in an ice bath, and treated dropwise with 50 ml of 2 *N* dimethylamine (0.10 mol) in tetrahydrofuran. The mixture was allowed to stand at room temperature for *ca.* 7 days and then concentrated *in vacuo*. The residue was treated with 100 ml of 5 *N* HCl and 50 ml of benzene. The acid layer was separated, cooled in an ice bath, and treated with 50% KOH until the aqueous phase had pH 9.0. The mixture was extracted with 50 ml of toluene, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give 3.1 g (25%) of **9** as a viscous oil: ir ($CHCl_3$) no OH bond; R_f 0.6 ($CHCl_3$–CH_3OH, 98:2).

Anal. Calcd for $C_{15}H_{16}ClN$: C, 73.5; H, 6.5; Cl, 14.5. Found: C, 73.3; H, 6.6; Cl, 14.3.

3-Methyl-2-phenyloxazolidine (10). A mixture of 13.1 g (0.123 mol) of benzaldehyde, 9.2 g (0.123 mol) of *N*-methylethanolamine and 50 ml of benzene were stirred and refluxed in a flask with a Dean–Stark water separator until the water level in the separator remained constant (*ca.* 1 hr). The mixture was distilled to give 17.1 g (85%) of **10**: bp 55° (1.0 mm); ir ($CHCl_3$), no C=O bond; tlc [$CHCl_3$–CH_3OH (98:2)], one component; lit.[12] bp 110–115° (18 mm).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.6; H, 8.0; N, 8.6. Found: C, 73.8; H, 7.9; N, 8.4.

1-Methyl-2-phenylimidazolidine (11). A mixture of 10.6 g (0.10 mol) of benzaldehyde, 7.5 g (0.10 mol) of *N*-methylethylenediamine, and 50 ml of benzene were treated as in the preparation of **9** to give 13 g (80%) of **11**: bp 100° (1.0 mm); ir ($CHCl_3$), no C=O bond; tlc [$CHCl_3$–CH_3OH (98:2)], one component.

Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.0; H, 8.7; N, 17.3. Found: C, 74.3; H, 8.8; N, 17.2.

Acknowledgments. The authors thank Mr. T. Doyle for synthetic assistance, Dr. Sandor Barcza for obtaining the ^{13}C nmr spectra, and Mr. W. Bonkowski for analytical determinations.

Registry No.—**1b**, 6038-49-9; **4**, 23227-06-7; **5**, 26800-10-2; **9**, 53370-25-5; **10**, 1630-62-2; **11**, 53370-26-6; $LiAlH_4$, 16853-85-3; THF, 109-99-9; 4-chlorobenzhydrol, 119-56-2; dimethylamine, 124-40-3; benzaldehyde, 100-52-7; *N*-methylethanolamine, 109-83-1; *N*-methylethylenediamine, 109-81-9.

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(5) Additional examples of the $LiAlH_4$–THF reduction of **1** can be found in (a) W. J. Houlihan, U. S. Patent 3,444,181, *Chem. Abstr.*, **71**, 49941n (1969); (b) W. J. Houlihan, Ger. Offen. Patent 1,814,540, *Chem. Abstr.*, **71**, 81368s (1969); (c) P. Aeberli, P. Eden, J. H. Gogerty, W. J. Houlihan, and C. Penberthy, *J. Med. Chem.*, in press.
(6) On several occasions, the nmr spectrum obtained in DMSO-d_6 gave this signal as a broad unresolved band.
(7) Compound **5** has also been prepared by treating **1b** with $LiAlH_4$ in diethyl ether at ambient temperature for 0.5 hr. The reported ir, nmr, and uv data are in excellent agreement with our findings. T. S. Sulkowski, Ger. Offen. Patent 1,926,477, *Chem. Abstr.*, **72**, 66920t (1970); T. S. Sulkowski, U. S. Patent 3,555,042.
(8) W. Metlesics, T. Anton, M. Chaykovsky, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **33**, 2874 (1968).
(9) Structure **6** has previously been incorrectly assigned to the $LiAlH_4$ reduction product of **1b** in THF: G. A. Cooke and W. J. Houlihan, Ger. Offen. Patent 2,023,633, *Chem. Abstr.*, **74**, 42360a (1971).
(10) It has been reported in ref 1 that use of THF or dioxane in the $LiAlH_4$ reduction of **1** results in considerably lower yields of **2** relative to use of refluxing diethyl ether. In the present work, we have been unable to detect the presence of any **2b** in our reduction product using tlc analyses.
(11) Melting points were determined in a Thomas-Hoover capillary melting point apparatus and have not been corrected. The ir spectra (KBr) were determined using a Perkin-Elmer Infracord and the uv spectrum on a Cary Model 15 spectrophotometer. The pmr spectra were obtained on a Varian Associates A-60 spectrometer. The ^{13}C nmr spectra were carried out on a Bruker HX-90 spectrometer equipped with a pulse-Fourier transform accessory that included a Fabritch (Nicolet) signal averager and a PDP-8 computer that contained 4K data points in the time domain. The frequency was set at 22.62 MHz with broad band ^1H decoupling at 90 MHz and typical sweep width of 5000 Hz with 15-μsec pulse width. Hexafluorobenzene was added for locking and hexamethyldisiloxane was used as an internal standard, which was taken as 191 ppm upfield of CS_2 and 2 ppm downfield of TMS. Thin layer chromatography (tlc) was carried out using glass plates coated with silica gel HF-254 (E. Merck AG).
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N-Alkylation of Purines with Alkyl Esters of Phosphorus Oxy Acids

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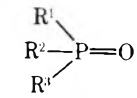
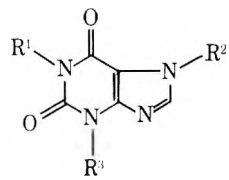
Although alkyl esters of sulfuric and sulfonic acids have been well studied and utilized as alkylating reagents,[1-3] there are few studies on alkylation reaction by alkyl esters of phosphorus oxy acids. We have previously shown that a trialkyl phosphate is an excellent reagent for the *N*-alkylation of pyrimidines[4] and imidazoles.[5] We have now extended the investigation to the *N*-alkylation of purines. Reactions were performed by heating a mixture of a purine and an excess of the ester, and the products were isolated through extraction and recrystallization. The results are summarized in Table I.

Thus, reactions of xanthine (**1**) with esters (**a, b, d, e**) brought about substitution at the 1, 3, and 7 positions to form 1,3,7-trialkyl- and 3,7-dialkylxanthines. Theophylline (**2**) was alkylated especially smoothly to furnish the corresponding 7-alkyl derivative in high yields. The reactions also revealed the following general order of alkylating power among phosphorus oxy acids; phosphate > phosphonate > phosphinate. Methylation of theobromine (**3**) and its ethyl analog (**4**) also took place easily at the 1 position to give **5** and **8**, but we were unable to ethylate these two compounds. The selective methylation at the 1-position of 3,7-dialkylxanthine may be attributed to the steric hindrance at the position or the lowered reactivity of ethyl esters.[5] Similar results in alkylation have been obtained in alkyl esters of sulfur oxy acids.[1,2]

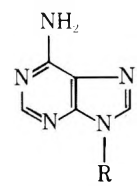
In the case of adenine (**9**), the preferential alkylation at the 3-position was observed to generate 3-alkyladenine (**10, 12**). Alkyl esters of sulfur oxy acids[2,3] and alkyl halides[6,7]



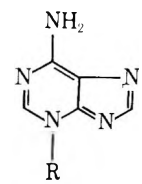
a, $R^1 = R^2 = R^3 = OMe$ **d**, $R^1 = R^2 = R^3 = OEt$
b, $R^1 = R^2 = OMe$; $R^3 = Me$ **e**, $R^1 = R^2 = OEt$; $R^3 = Et$
c, $R^1 = OMe$; $R^2 = R^3 = Me$ **f**, $R^1 = OEt$; $R^2 = Et$; $R^4 = Ph$



1, $R^1 = R^2 = R^3 = H$ **5**, $R^1 = R^2 = R^3 = Me$
2, $R^1 = R^3 = Me$; $R^2 = H$ **6**, $R^1 = R^2 = R^3 = Et$
3, $R^1 = H$; $R^2 = R^3 = Me$ **7**, $R^1 = R^3 = Me$; $R^2 = Et$
4, $R^1 = H$; $R^2 = R^3 = Et$ **8**, $R^1 = Me$; $R^2 = R^3 = Et$



9, R = H
11, R = Et



10, R = Me
12, R = Et

also have been reported to produce 3-alkyladenine preferentialy, whereas the reaction of alkyl halide with **9** in the presence of a base or with a sodium salt of **9** have been known to afford 9-alkyl derivative as a major product.

Those results indicate that the present procedure using alkyl esters of phosphorus oxy acids, especially a trialkyl phosphate, may be very useful for *N*-alkylation of purines.

Experimental Section

Uv and ir spectra were measured with Hitachi-3T, and Jasco IR-G spectrometers, respectively. Proton nmr spectra were recorded

Table I
Reactions of Purines with Alkyl Esters of Phosphorus Oxy Acids

Purine, P	Ester, E	Mole ratio, E/P	React. temp	React. time, hr	Product	Yield, %
Xanthine (**1**)	a	5	190	1.5	1,3,7-Trimethylxanthine (**5**)[a]	50
	b	5	190	2.5	**5**	51
	d	3	200	10.0	1,3,7-Triethylxanthine (**6**)	22
					3,7-Diethylxanthine (**4**)	25
	e	2	200	10.0	**6**	37
					4	39
Theophylline (**2**)	a	1.3	180	1.0	**5**	90
	b	1.3	190	5.0	**5**	98
	c	1.3	190	11.0	**5**	82
	d	3	180	1.3	7-Ethyl-1,3-dimethylxanthine (**7**)	79
	e	3	180	4.0	**7**	70
	f	3	210	2.0	**7**	90
Theobromine (**3**)	a	6	190	1.5	**5**	79
	b	3	190	11.0	**5**	77
	d	6	190	12.0	No reaction	
3,7-Diethyl-xanthine (**4**)	a	3	180	16.0	3,7-Diethyl-1-methylxanthine (**8**)	72
	b	5	190	16.0	**8**	65
	d	5	190	15.0	No reaction	
Adenine (**9**)[b]	a	1	140	2.0	3-Methyladenine (**10**)	45
	b	1	140	9.0	**10**	61
	d	1	140	4.0	3-Ethyladenine (**12**)	30
					9-Ethyladenine (**11**)	15
	e	1	140	13.0	**12**	13
					11	10

[a] Caffeine. [b] DMF was used as a solvent in the reactions.

on a Hitachi–Perkin Elmer R-20 spectrometer with a dilute solution in deuterochloroform, and tetramethylsilane as an internal standard.

Materials. Commercially available xanthine, theophylline, theobromine, and adenine, as well as trimethyl and triethyl phosphates were used without further purification. Dimethyl methyl- and diethyl ethylphosphonates were prepared quantitatively *via* Arbuzov reactions using the corresponding trialkyl phosphites and alkyl iodides.[10] Methyl dimethyl- and ethyl ethylphenylphosphinates were obtained by the procedure of Reinhardt, *et al.*,[11] and Steininger,[12] respectively. Reaction conditions are listed in Table I. The following preparations are typical.

Alkylation of Xanthine (1). A. With Trimethyl Phosphate (a). A mixture of 1 (3.0 g, 0.02 mol) and **a** (14.0 g, 0.1 mol) was refluxed with stirring. The light-boiling substances were removed from the resulting clear solution under reduced pressure to give a residue, which was then dissolved in chloroform, and the solution was neutralized with an aqueous solution of sodium hydrogen carbonate. Evaporation of the solvent from the organic solution gave caffeine (5) as crystals: 1.90 g (50%); mp 223–234° (tetrahydrofuran–diethyl ether) (lit.[13] mp 235°); λ_{max} (H_2O) 272 nm (log ϵ 4.04) [lit.[13] λ_{max} (H_2O) 272 nm (log ϵ 4.03)].

B. With Triethyl Phosphate (d). Compound (1) (3.25 g, 0.02 mol) and **d** (11.68 g, 0.06 mol) afforded the following two products after preparative thin layer chromatography (2-mm thickness, Silica gel G according to Stahl, E. Merck, Darmstadt, West Germany) of the chloroform extract, which was obtained from the reaction mixture in a manner similar to that mentioned above. A mixture of ether and ethanol (15:1) was employed as a developing solvent.

3,7-Diethylxanthine (4): 1.1 g (25%); R_f 0.5; mp 179–182° (H_2O) (lit.[14] mp 183°); ir (KBr) 3150 (w), 2980 (m), 1680 (s), 1540 (m), 1445 (w), 1275 (w), 1220 (w), 1030 (m), and 850 (m) cm^{-1}; nmr ($CDCl_3$) δ 8.90 (s, 1, NH), 7.50 (s, 1, ring H), 4.25 (q, 2, CH_2), 4.10 (q, 2, CH_2), 1.50 (t, 3, CH_3), and 1.32 (t, 3, CH_3).

1,3,7-Triethylxanthine (6): 1.1 g (22%); R_f 0.8; mp 108–111° (H_2O) (lit.[15] mp 111°); ir (KBr) 3100 (w), 2980 (w), 1700 (s), 1650 (s), 1545 (m), 1450 (m), 1230 (w), 1050 (w), 1020 (w), 875 (m), and 750 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.45 (s, 1, ring H), 3.7–4.5 (complex m, 6, 3 CH_2) and 1.0–1.6 (complex m, 9, 3 CH_3).

Ethylation of Theophylline (2) with d. A mixture of 2 (3.46 g, 0.02 mol) and **d** (10.50 g, 0.06 mol) was heated at 180° for 1.3 hr. The reaction mixture was treated in a manner similar to the methylation of 1 to give 3.12 g (79%) of 7-ethyl-1,3-dimethylxanthine (7): mp 148–149° (ethanol) (lit.[2] mp 152–153°); ir (KBr) 3100 (w), 2980 (w), 1700 (s), 1650 (s), 1545 (m), 1480 (m), 1220 (m), 1190 (m), 1020 (w), 970 (m), and 740 (m) cm^{-1}; nmr ($CDCl_3$) δ 7.46 (s, 1, ring H), 4.35 (q, 2, CH_2), 3.62 (s, 3, NCH_3), 3.45 (s, 3, NCH_3) and 1.55 (t, 3, CH_3).

Methylation of 3,7-Diethylxanthine (4) with a. Compound 4 (1.0 g, 0.005 mol) was treated with excess of **a** to produce 0.8 g (72%) of 3,7-diethyl-1-methylxanthine (8): mp 96° (sublimed); ir (KBr) 3100 (w), 1700 (s), 1650 (s), 1545 (m), 1490 (m), 1230 (m), 1000 (m), and 750 (m) cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.25; H, 6.18; 24.42.

Alkylation of Adenine (9). A. With a. A mixture of 9 (1.50 g, 0.01 mol) and **a** (1.40 g, 0.01 mol) in dimethylformamide (10 ml) was refluxed for 2 hr. The reaction mixture was allowed to stand overnight to yield crystals which was dissolved in aqueous sodium hydrogen carbonate and the solution was concentrated to dryness. Extraction of the residue with ethanol and evaporation of the solvent afforded 3-methyladenine (10) as crystals: 0.75 g (45%); mp 300° (water) (lit.[16] mp 302°); λ_{max} (H_2O) 274 nm (log ϵ 4.17) [lit.[16] λ_{max} (H_2O) 274 nm (log ϵ 4.21)].

B. With d. Adenine (1.50 g, 0.01 mol) and **d** (2.0 g, 0.01 mol) were refluxed in dimethylformamide (8 ml) for 4 hr. The solvent was evaporated under reduced pressure to give a residue, which was then dissolved in aqueous hydrogen carbonate and concentrated as much as possible. The resulting residue in ethanol was chromatographed on alumina (2 cm × 30 cm, 300 mesh, neutral). Elution with a mixture of ethyl acetate and methanol (10:1) gave 0.2 g (15%) of 9-ethyladenine (11): mp 193° (ethyl acetate–ether) (lit.[17] mp 194–195°); λ_{max} (H_2O) 260.0 nm (log ϵ 4.13) [lit.[17] λ_{max} (H_2O) 262 nm (log ϵ 4.15)].

Subsequent elution with the same solvent afforded 0.5 g (30%) of 3-ethyladenine (12): mp 229–232° (lit.[16] mp 233°); λ_{max} (H_2O) 274.5 nm (log λ 4.15) [lit.[16] λ_{max} (H_2O) 273 nm (log ϵ 4.04)].

Registry No.—**1**, 69-89-6; **2**, 58-55-9; **3**, 83-67-0; **4**, 53432-04-5; **5**, 58-08-2; **6**, 31542-50-4; **7**, 23043-88-1; **8**, 53432-05-6; **9**, 73-24-5; **10**, 5142-23-4; **11**, 2715-68-6; **12**, 43003-87-8; **a**, 512-56-1; **b**, 756-79-6; **c**, 14337-77-0; **d**, 78-40-0; **e**, 78-38-6; **f**, 2227-43-2.

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Synthesis of Furoguaiacidin Diethyl Ether

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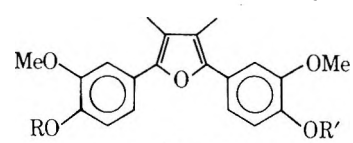
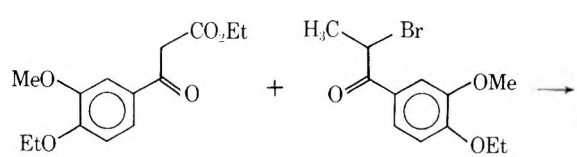
From "lignum vitae", the heartwood of *Guaiacum officinale*, King and Wilson[1] isolated and identified nine lignans including furoguaiacin [as the dimethyl ether (1)] and methylfuroguaiacin [as the ethyl ether (2)]. Until recently,



1, R = R′ = Me
2, R = Me; R′ = Et



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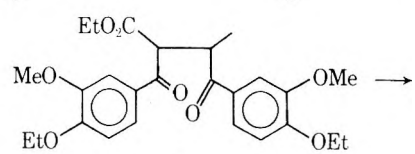

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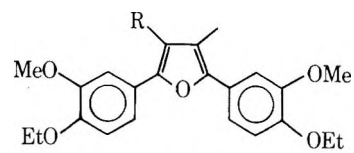

3, R = CH_2OMe
7, R = CO_2Et
8, R = CH_2OH

when a third member named furoguaiacidin was isolated (as the diethyl ether) by Majumder and Bhattacharyya[2] from the same source, these were the only known examples of lignans possessing the furan heterocycle system.

We now report a short synthesis of 2,5-bis(4-ethoxy-3-methoxyphenyl)-4-methoxymethyl-3-methylfuran (**3**), the structure proposed for furoguaiacidin diethyl ether. Alkylation of ethyl 4-ethoxy-3-methoxybenzoylacetate (**4**) with α-bromo-4-ethoxy-3-methoxypropiophenone (**5**) using sodium hydride gave the diketo ester (**6**) which, without isolation, was converted to the required furan, ethyl 2,5-bis(4-ethoxy-3-methoxyphenyl)-3-methylfuran-4-carboxylate (**7**). Reduction of this ester with lithium aluminum hydride gave the alcohol (**8**) which on alkylation with methyl iodide–sodium hydride in dimethoxyethane gave the product, furoguaiacidin diethyl ether (**3**) with physical constants (mp, nmr, ir, uv) in excellent agreement with those reported.

Experimental Section

Nmr spectra were measured in deuteriochloroform solution with tetramethylsilane as internal standard.

Ethyl 4-Ethoxy-3-methoxybenzoylacetate (4). A previously described procedure[3] was modified by using sodium hydride instead of sodium ethoxide and reducing the reaction time from 60 hr to 30 min: nmr δ 1.23 (t, 3 H, J = 7 Hz, $-CO_2CH_2CH_3$), 1.47 (t, 3 H, J = 7 Hz, $ArOCH_2CH_3$), 3.87 (s, 3 H, OCH_3), 3.90 (s, 2 H, CH_2), 4.13 (q, 2 H, J = 7 Hz, $ArOCH_2CH_3$), 4.17 (q, 2 H, J = 7 Hz, $-CO_2CH_2CH_3$), 6.75–7.57 (m, 3 H, ArH).

α-Bromo-4-ethoxy-3-methoxypropiophenone (5) was crystallized from methanol and had mp 72–73° (lit.[4] 76–77°); nmr δ 1.47 (t, 3 H, J = 7 Hz, $ArOCH_2CH_3$), 1.85 (d, 3 H, J = 6.5 Hz, CH_3CHBr), 3.88 (s, 3 H, OCH_3), 4.16 (q, 2 H, J = 7 Hz, $ArOCH_2CH_3$), 5.29 (q, 1 H, J = 6.5 Hz, $CH_3CHBrCO$), 6.78–7.62 (m, 3 H, ArH).

Ethyl 2,5-Bis(4-ethoxy-3-methoxyphenyl)-3-methylfuran-4-carboxylate (7). Sodium hydride (122 mg, 57% oil dispersion) was added with stirring to absolute ethanol (50 ml) under nitrogen, followed by a solution of the keto ester **4** (770 mg) in the same solvent (25 ml). This mixture was stirred for 15–20 min, and a solution of the bromo ketone **5** (830 mg) in ethanol (25 ml) was added dropwise. The flask was then stoppered and stirred at room temperature for 3 days. Hydrogen chloride gas was bubbled through the reaction mixture for 20 min at 0°, then the resulting dark solution refluxed for 1 hr, poured into water (300 ml), and extracted with chloroform. Removal of the solvent and crystallization of the dark residue from methanol gave the furan ester (**7**) as pale yellow prisms (550 mg): mp 113–115°; nmr δ 1.32 (t, 3 H, J = 7 Hz, $-CO_2CH_2CH_3$), 1.47 (t, 6 H, J = 7 Hz, $ArOCH_2CH_3$), 2.38 (s, 3 H, CH_3), 3.92 (s, 6 H, OCH_3), 4.14 (q, 4H, J = 7 Hz, $ArOCH_2CH_3$), 4.33 (q, 2 H, J = 7 Hz, $-CO_2CH_2CH_3$), 6.83–7.57 (m, 6 H, ArH).

Anal. Calcd for $C_{26}H_{30}O_7$: C, 68.70; H, 6.65. Found: C, 68.80; H, 6.68.

2,5-Bis(4-ethoxy-3-methoxyphenyl)-4-hydroxymethyl-3-methylfuran (8). A solution of the ester **7** (149 mg) in ether (15 ml) was added with stirring to lithium aluminum hydride (*ca.* 0.5 g) in ether (30 ml) at 0° under nitrogen. The mixture was allowed to reach room temperature on standing overnight, then decomposed by addition of ethyl acetate, then water until coagulation occurred. The solution was decanted, dried ($MgSO_4$), and evaporated to yield the alcohol **8**, crystallized from methanol as colorless needles: mp 147–148°; nmr δ 1.45 (t, 6 H, J = 7 Hz, $ArOCH_2CH_3$), 2.03 (br s, 1 H, –OH), 2.25 (s, 3 H, CH_3), 3.88 (s, 6 H, OCH_3), 4.09 (q, 6 H, J = 7 Hz, $ArOCH_2CH_3$), 4.62 (s, 2 H, CH_2OH), 6.80–7.52 (m, 6 H, ArH).

Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.80; H, 6.90.

Furoguaiacidin Diethyl Ether (3). To a stirred solution of the alcohol **8** (547 mg) in dry 1,2-dimethoxyethane (25 ml) was added methyl iodide (10 drops) and sodium hydride (*ca.* 10 mg, 57% oil dispersion) under nitrogen. More methyl iodide (25 drops) was then added and the mixture stirred overnight at room temperature. Removal of the solvent under reduced pressure gave a yellow-green crystalline residue, which was dissolved in chloroform, washed with water, and dried. Removal of the colored impurity was effected by preparative tlc (silica gel, Merck PF 254+366) using benzene–acetone (9:1) to give furoguaiacidin diethyl ether (**3**) as colorless prisms (290 mg) from methanol: mp 133.5–135° (lit.[2] mp 135°); λ(C_2H_5OH) 258 nm (log 4.47) and 324 (4.16); nmr δ 1.45 (t, 4 H, J = 7 Hz, $ArOCH_2CH_3$), 2.27 (s, 3 H, CH_3), 3.45 (s, 3 H, $-CH_2OCH_3$), 3.92 (s, 6 H, $ArOCH_3$), 4.12 (q, 4 H, J = 7 Hz, $ArOCH_2CH_3$), 4.40 (s, 2 H, CH_2OCH_3), and 6.83–7.37 (m, 6 H, ArH).

Acknowledgment. This investigation was supported by a research grant (GM 19566) from the National Institutes of General Medical Sciences, U.S. Public Health Service.

Registry No.—**3**, 52465-56-2; **4**, 53293-05-3; **5**, 721-42-6; **7**, 53293-06-4; **8**, 53293-07-5.

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Anomalous Reaction of Selenium and Carbon Disulfide with Sodium Acetylide. Synthesis of Selenium Analogs of 1,3-Dithiole-2-thione[1]

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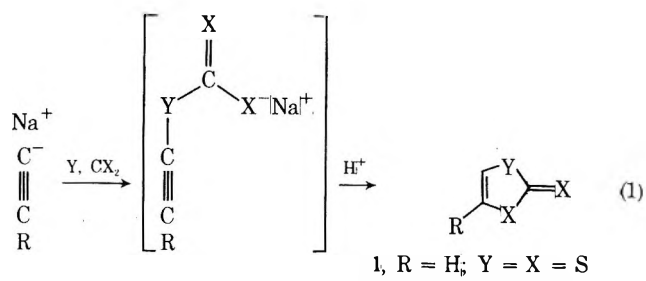
In 1964, Mayer and Gebhardt[2] reported a simple one-step synthesis of 1,3-dithiole-2-thione (**1**) which involved the addition of sulfur and carbon disulfide to sodium acetylide (eq 1). This procedure was subsequently extended with



(1)

1, R = H; Y = X = S
2, R = C_6H_5; Y = Se; X = S
3, R = CH_3; Y = Se; X = S

the preparation of 5-phenyl-1,3-thiaselenole-2-thione (**2**).[3] We report here the anomalous reaction that occurs in the attempt to prepare the parent compound of **2** by this method.

Treatment of sodium acetylide with selenium and carbon disulfide gave, in addition to the expected product, 1,3-thiaselenole-2-thione (**4**), four other related compounds identified as **1**, 1,3-dithiole-2-selone (**5**), 1,3-thiaselenole-2-selone (**6**), and 1,3-diselenole-2-thione (**7**). In a similar reaction, sulfur and carbon diselenide reacted with sodium acetylide to give the same products as well as 1,3-diselenole-2-selone (**8**). Table I lists the relative percentages of the products formed in these two reactions. The products were easily separated by chromatography on silica gel (5% $CHCl_3$ in CCl_4). Relative to **1**, the introduction of selenium into the ring reduces the retention time on the column, while replacement of the thiocarbonyl in **1** with a selenocarbonyl increases it. In a compound such as **6**, the selenium in the carbonyl has a greater effect on the retention time than in the ring, and this material is eluted after **1**.

Table I
Relative Per Cent Composition

Reaction	Relative % composition[a]					
NaC≡CH $\xrightarrow[2.\ H^+]{1.\ Y,\ CX_2}$	 1	 4	 5	 6	 7	 8
Y = Se; X = S	22	70	5	2	1	0
Y = S; X = Se	1	1	15	25	8	50

[a] Approximate values based on amounts of material isolated after chromatography and from analysis by high-pressure liquid chromatography.

Table II
Spectroscopic Properties

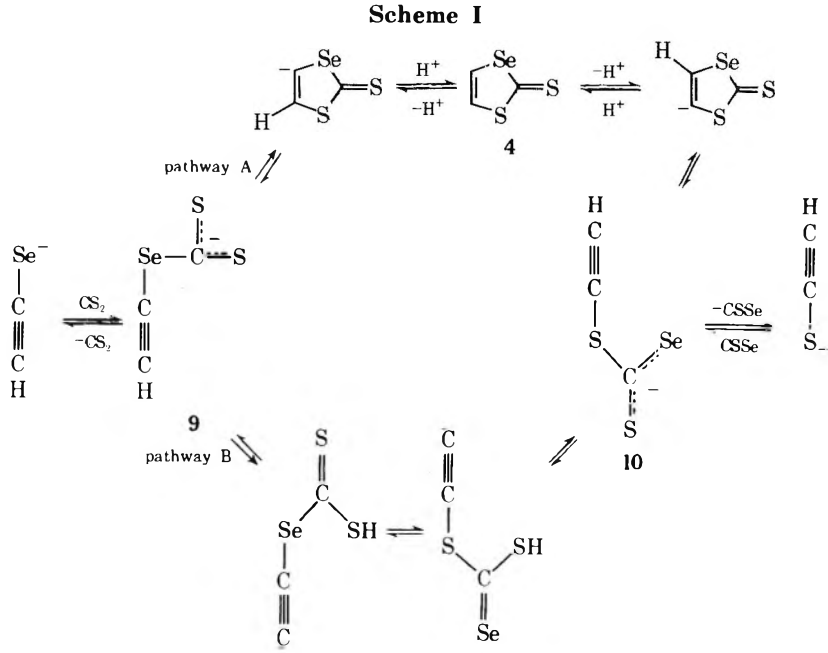
Measurement	1	4	7	5	6	8
Ir (CCl_4, cm^{-1})	1070, 1100	1060, 1095	1040, 1086	960	940	920
Nmr (δ, rel to TMS, $CDCl_3$)	7.17	7.26, 7.80 (J_{AB} = 7.5 Hz)	7.92	7.35	7.42, 8.01 (J_{AB} = 7.5 Hz)	8.10
Uv–visible, λ (ε) (hexane)	430 (100)	440 (100)	455 (100)	530 (300)	548 (270)	555 (400)
	360 (11,000)	368 (15,500)	377 (12,100)	402 (11,800)	410 (13,100)	413 (14,100)
	275 (1000)	285 (2600)	290 (1850)	295 (1000)	305 (1500)	318 (1200)
	230 (5500)	245 (10,700)	254 (9100)	233 (4700)	252 (6100)	264 (7200)

The identification of the products in these reactions follows from their spectroscopic properties (Table II), mass spectra, and elemental analyses.[4] The ir, nmr, and uv–visible data, collected on compounds **1** and **4–8** (Table II), display remarkable additive trends for the successive introduction of selenium into **1**, which shifts the spectroscopic absorptions to lower energies. Compound **1** was identified in comparison with literature values for this material.[1,5] Compounds **7** and **8** could be prepared by independent routes: addition of selenium and carbon diselenide to sodium acetylide provided **8**, while treatment of **8** with P_4S_{10} gave **7**.

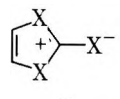
Two plausible mechanisms for the formation of the products listed in Table I are outlined in Scheme I. Pathway A involves ring closure of **9**, followed by addition and removal of H^+, and ring opening to give **10** in which a mixing of sulfur and selenium atoms has occurred. Alternately, the interconversion of **9** and **10** could be accomplished by the series of steps outlined by pathway B.[6] The formation of only one product in the case of phenyl substitution (**2**, eq 1) lends support for the two proposed mechanisms. The substituent effectively blocks the interconversion of **9** and **10**. This was further tested by treating sodium methylacetylide with selenium and carbon disulfide, which also yielded only one product, identified as 5-methyl-1,3-thiaselenole-2-thione (**3**).

Since pathway A involves removal of H^+ from the neutral ring closed product **4**, the preparation of **1** (eq 1) was carried out in the presence of **8** in order to check for the formation of mixed sulfur–selenium products. Analysis of the product mixture showed the expected presence of **1** (~95% of the product mixture), as well as **4** (~4%) and **7** (~1%). No **8** could be detected in the product mixture. While these results cannot rule out the operation of pathway B, no mixing of sulfur and selenium to give **4** and **7** would have strongly weighed against pathway A.

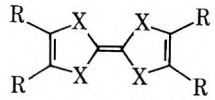
Scheme I



The reactions reported here provide an excellent opportunity to study the comparative reactivities and properties of sulfur and selenium in organic compounds. Furthermore, 1 and 4–8 are of interest as potential 6π-pseudo-aromatic systems in which each ring heteroatom contributes an electron pair as illustrated by the resonance structure 11.[7] Synthetically, these compounds have gained attention as intermediates in the preparation of tetrathiofulvalene derivatives (12) which have recently been reported to form highly conducting charge-transfer salts.[8-11]



11



12

Experimental Section

General. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Molecular ion values (*m/e*) reported for compounds containing selenium are based on ^{80}Se. Some of the selenium compounds involved in the synthetic procedures described herein (*e.g.*, CSe_2 and H_2Se) are extremely toxic and difficult to control, and appropriate precautions should be exercised in handling such materials.

Reaction of Sodium Acetylide with Selenium and Carbon Disulfide. A 1-l., three-necked flask, equipped with an efficient mechanical stirrer, Dry Ice condenser, and gas inlet for acetylene was placed in a Dry Ice bath and 300 ml of ammonia added. While acetylene was being bubbled through the ammonia, 4.6 g of sodium (0.2 g-atom) was added in small portions. After the sodium had reacted, the Dry Ice bath was removed, and 200 ml of anhydrous ether and 15.8 g of powdered selenium (0.2 g-atom) were added with vigorous stirring. The ammonia was allowed to evaporate and 300 ml of acetonitrile added. Carbon disulfide (15.2 g, 0.2 mol) in 100 ml of ether was added dropwise over 1 hr. The reaction was stirred for 1 hr more, and acidified with 10% aqueous HCl. The mixture was then extracted several times with ether[12] and dried ($MgSO_4$) and the ether removed. The remaining tarry material was extracted with several portions of hot methylcyclohexane[13] from which crystallized 2.8 g of a yellow-orange solid. Column chromatography (3 ft, silica gel column, 5% $CHCl_3$ in CCl_4 eluent) on this material easily separated five products which were further purified either by recrystallization (hexane) or sublimation. Characterization of the products is based on their ir, nmr, and uv–visible spectra (see Table II), mass spectra, and elemental analyses[4] and they are the following. 1,3-Dithiole-2-thione (1): yellow solid; mp 49.5° (lit. 48.4°,[1] 50°[4]); *m/e* 13.4; 1,3-Thiaselenole-2-thione (4): yellow solid; mp 60.5°; *m/e* 182; 1,3-Dithiole-2-selone (5): orange solid; mp 59–60°; *m/e* 182; 1,3-Thiaselenole-2-selone (6): orange solid, mp 80–81°; *m/e* 230; 1,3-Diselenole-2-thione (7): yellow solid; mp 83–84°; *m/e* 230.

Reaction of Sodium Acetylide with Sulfur and Carbon Diselenide. The same experimental conditions as described above were followed. However, extreme care should be taken due to the high toxicity and foul smell of carbon diselenide.[14] On a 0.2 mol preparative scale, 1.5 g of a red solid was isolated from which were separated compounds 1 and 4–7 and also 1,3-diselenole-2-selone (8): red solid; mp 113.5–114°; *m/e* 278 (see Table II for ir, nmr, and uv-visible data).

Reaction of Sodium Acetylide with Selenium and Carbon Diselenide. The same experimental conditions as described above were followed to give 8 in yields varying from 10 to 25%.

Reaction of 1,3-Diselenole-2-selone (8) with P_4S_{10}. To 0.275 g of 8 (1 mmol) in 15 ml of benzene was added 1.0 g of P_4S_{10} (Pfaltz and Bauer) with stirring, and the solution was refluxed for 3 hr. Work-up consisted of filtering, adding ether, washing with $NaHCO_3$, and drying ($MgSO_4$). Evaporation of the ether gave a yellow-brown solid which was placed on a short silica gel column, and eluted with 5% $CHCl_3$ in CCl_4 to give a bright yellow solid identified as 1,3-diselenole-2-thione (7) in 25% yield.

Reaction of Sodium Methylacetylide with Selenium and Carbon Disulfide. The same experimental conditions as described above were followed to give, on a 0.2 mol preparative scale, 6.5 g of 5-methyl-1,3-thiaselenole-2-thione (3) (25% yield) as a yellow-orange solid: mp 34–35°; ir ($CDCl_3$) 1060 cm^{-1}; nmr (δ, rel to TMS, CCl_4) 2.28 (3 H, doublet), 7.20 (1 H, quartet), $J_{allylic}$ = 1.5 Hz; *m/e* 196.

Reaction of Sodium Acetylide with Sulfur and Carbon Disulfide in the Presence of 8. The same experimental conditions as described above were followed on a 0.1 mol preparative scale, except that during the addition of carbon disulfide, 8 (0.1 g) was also added. High-pressure liquid chromatography revealed the presence of three products which were subsequently separated by column chromatography (5% $CHCl_3$ in CCl_4, silica gel) and identified by their ir and nmr spectra as 1 (~95% of product mixture), 4 (~4%), and 7 (~1%).

Acknowledgment. We thank D. Green for helpful discussions.

Registry No.—1, 930-35-8; 3, 53555-43-4; 4, 1120-65-6; 5, 53555-44-5; 6, 53555-45-6; 7, 53555-46-7; 8, 53555-47-8; sodium acetylide, 1066-26-8; selenium, 7782-49-2; carbon disulfide, 75-15-0; carbon diselenide, 506-80-9; sulfur, 7704-34-9; sodium methylacetylide, 10486-71-2.

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(12) Some difficulty was experienced in distinguishing the water–ether layer during the extraction step. An alternate work-up procedure has been developed by Dr. F. Wudl, Bell Laboratories, Murray Hill, N.J., which involves extraction of the acidified reaction mixture with a lighter-than-water liquid–liquid extractor, and extraction with hexane over a period of several hours.
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A Simple Synthesis of γ-Bisabolene

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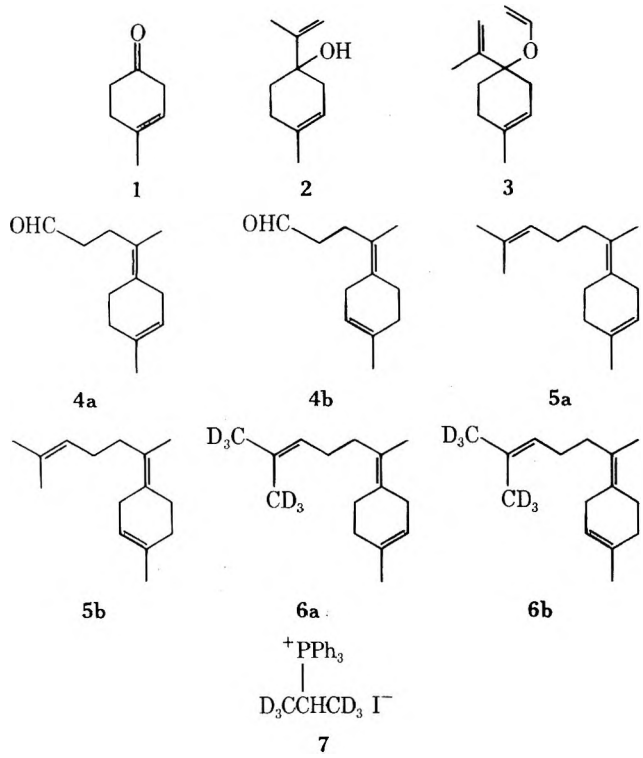
Received March 12, 1974

To pursue our research on the biosynthesis of marine natural products, we were obliged to synthesize γ-bisabolene. Our choice of synthetic strategies was limited because we required the capability of incorporating isotopic labels during the penultimate stages of the synthesis. We explored the only previous stereoselective synthesis of γ-bisabolene[1] but could not repeat a key reaction to our satisfaction. We have therefore devised a simple synthesis of γ-bisabolene based on the Claisen rearrangement. Hexadeuterio-γ-bisabolene was also prepared by this route.

4-Methyl-3-cyclohexen-1-one (1), prepared from *p*-cresol by the method of Braude and Webb,[2] was treated with



isopropenylmagnesium bromide in tetrahydrofuran solution at 0° to obtain the allylic alcohol (**2**) in 43% yield. The use of isopropenyllithium in this reaction caused the formation of 4-methyl-2-cyclohexen-1-one, which then underwent various side reactions. The alcohol **2** was converted into the corresponding vinyl ether **3** in 74% yield using the mercuric acetate catalyzed transetherification reaction.[3] Pyrolysis of the allyl vinyl ether **3** resulted in an almost quantitative conversion to the aldehyde **4** *via* the Claisen rearrangement.

Since the mercuric acetate catalyzed transetherification reaction was not reproducible, we investigated the possibility of combining the transetherification and pyrolysis reactions in order to remove the allyl vinyl ether **3** as it was formed and drive the transetherification reaction to completion. Acid catalyzed transetherification reactions[4] gave poor yields of the aldehyde **4** since the product underwent further reactions. The best conditions we found for this sequence involved heating the allylic alcohol **2** with 10 equiv of ethyl vinyl ether in the presence of 1 equiv of mercuric acetate and 2 equivalents of anhydrous sodium acetate under an argon atmosphere in a sealed tube at 100° for 16 hr.[5] Under these conditions an 81% yield of the aldehyde **4** was isolated after distillation. A Wittig reaction between the aldehyde **4** and isopropyltriphenylphosphonium ylide gave γ-bisabolene (**5**) in 45% yield.

The existence of two geometrical isomers of γ-bisabolene (**5a** and **5b**) has generally been ignored by previous investigators. The two γ-bisabolenes, isomeric about the tetrasubstituted olefinic bond, may be designated as (*E*)-γ-bisabolene (**5a**) and (*Z*)-γ-bisabolene (**5b**). The formation of both aldehydes **4a** and **4b** is a predictable outcome of the Claisen rearrangement. Thus our synthetic γ-bisabolene (**5**) was a mixture of both geometrical isomers in the ratio 60:40. The (*E*)- and (*Z*)-γ-bisabolenes may be separated by vpc on a 6-ft column of 2% Carbowax 20M or by spinning-band distillation. We have not found any spectral feature which permitted a structural assignment of the two stereoisomers.

The hexadeuterio-γ-bisabolenes (**6a** and **6b**) were prepared by the reaction of the aldehyde **4** with hexadeuterioisopropyltriphenylphosphonium ylide (**7**), which was, in turn, prepared from hexadeuterioisopropyl alcohol *via* hexadeuterioisopropyl iodide.[6] Only two peaks in the mass spectrum of hexadeuterio-γ-bisabolene (M^+ 210, $C_5H_3D_6$ 75) differ from those of γ-bisabolene (M^+ 204, C_5H_9 69) but this difference is sufficient to allow the detection of unlabeled γ-bisabolene in a hexadeuterio-γ-bisabolene carrier,[7] permitting its use in biosynthetic studies.

Experimental Section

Nmr spectra were obtained on Varian HR-220, T-60, or EM-360 spectrometers; infrared spectra on a Perkin-Elmer 700 spectrometer. Boiling points are uncorrected. Gas chromatographic analyses were performed on a Hewlett-Packard 402 instrument.

4-Methylcyclohex-3-enone (1) (The method of Braude and Webb[2]). A solution of redistilled *p*-methoxytoluene (61 g, 0.5 mol) in anhydrous ethyl ether (300 ml) was added to liquid ammonia (800 ml). After 15 min, small pieces of lithium wire (13.2 g, 1.9 equiv) were added over a 30-min period. Stirring was continued for 15 min, then ethanol (96.5 g, 2.1 mol) was added dropwise. Following addition of alcohol, the blue color disappeared and the ammonia was allowed to evaporate overnight. Ice (375 g) was added to residue, followed by a little water. The mixture was extracted with ether. The combined ether extracts were washed with water and concentrated to approximately 200 ml. The ether layer was stirred overnight with aqueous 2*M* oxalic acid (200 ml). The ether layer was separated, washed successively with sodium bicarbonate and water, dried over sodium sulfate, and distilled to obtain 4-methyl-3-cyclohexenone as a clear oil: bp 70–73° (20 mm), lit[2] bp 74° (17 mm); yield 49.6 g (89%); ir (film) 1720, 785 cm^{-1}; nmr (CCl_4) δ 1.80 (s, 3 H), 2.42 (s, 4 H, broad), 2.73 (s, 2 H, broad), 5.21 (t, 1 H).

4-Isopropenyl-4-hydroxy-1-methylcyclohexene (2). Magnesium metal shavings (3.645 g, 0.15 g-atom) were placed in a 250-ml 3-neck round-bottom flask equipped with a reflux condenser, a mechanical stirrer, and an additional funnel. The system was flushed with nitrogen for 15 min before addition of tetrahydrofuran (5 ml). A small volume of 2-bromopropene was added to the stirred solution. Glass chips were placed in the flask to help initiate the reaction. Once the reaction had started, the remainder of the bromide (18.1 g, 0.15 mol) in tetrahydrofuran solution (50 ml) was added. The reaction mixture was kept at <20° throughout addition. After approximately 1 hr, the brown solution was cooled to 0° with an ice-salt bath and the cyclohexenyl ketone (11.0 g, 0.1 mol) was added dropwise. The temperature was kept below 5° throughout addition. The reaction mixture was stirred for 3 hr at room temperature. The solution was poured into ice-cold ammonium chloride solution and extracted with ether. The extracts were combined and dried over anhydrous sodium sulfate and distilled to give 4-isopropenyl-4-hydroxy-1-methylcyclohexene: bp 85° (1 mm); yield 6.5 g (43%); ir (film) 3450, 1650, 1450, 1380, 910 cm^{-1}; nmr (CCl_4) δ 1.71 (s, 3 H), 1.80 (s, 3 H), 2.42 (s, 1 H), 4.72 (s, 1 H), 4.95 (s, 1 H), 5.25 (t, broad, 1 H); high resolution mass spectrum M^+ 152.1200, $C_{10}H_{16}O$ requires 152.1201.

4-Isopropenyl-1-methyl-1-cyclohexen-4-yl Vinyl Ether (3) (*cf.* Church, *et al.*[3]). 4-Isopropenyl-4-hydroxy-1-methylcyclohexene (**2**, 3.450 g, 22.6 mmol), mercuric acetate (7.20 g, 22.6.6 mmol, freshly recrystallized from ethanol containing a trace of acetic acid), and ethyl vinyl ether (200 ml, freshly distilled from sodium metal) were boiled under reflux for 48 hr under a nitrogen atmosphere. The mixture was cooled, glacial acetic acid (0.5 ml) was added, and the mixture was again stirred for 24 hr at room temperature. An equal volume of petroleum ether (30–60°) was added and the solution was washed with 5% potassium hydroxide solution (2 × 200 ml) and water (200 ml), then dried over anhydrous potassium carbonate. The petroleum-ether mixture was evaporated to a small volume (10 ml) which was placed on a 1 × 2 in. column of neutral alumina. Elution with petroleum ether (150 ml) afforded 4-isopropenyl-1-methyl-1-cyclohexen-4-yl vinyl ether: yield 2.96 g (74%); ir (film) 1635, 1185 cm^{-1}; nmr (CCl_4) δ 1.69 (s, 3 H), 1.75 (s, 3 H), 1.90 (s, broad, 4 H), 2.21 (multiplet 2 H), 3.89 (d, 1 H, J = 4 Hz), 4.25 (d, 1 H, J = 4 Hz), 4.90 (s, 2 H), 5.20 (t, 1 H), 6.08 (double doublet 1 H, J = 14, 4 Hz).

4-Methyl-1-(1′-propanalethylidene)-3-cyclohexene (4a, 4b). 4-Isopropenyl-1-methylcyclohex-1-en-4-yl vinyl ether (2.96 g, 16 mmol) was dissolved in dry toluene (10 ml) and heated at 110° for 2 hr, after which thin layer chromatography showed disappearance of the vinyl ether. Kugelrohr distillation of the product gave the pure aldehyde, 4-methyl-1-(1′-propanalethylidene)-3-cyclohexene:

bp 96° (0.1 mm); yield 2.53 g (86%); ir (film) 2740, 1725, 740 cm^{-1}; nmr (CCl_4) δ 1.65 (s, 6 H), 2.39 (s, 4 H, broad), 2.68 (3, 2 H), 5.28 (t, 1 H), 9.70 (d, 1 H); high resolution mass spectrum M^+ 178.1359, $C_{12}H_{18}O$ requires 178.1358. The aldehyde consisted of a 41:59 ratio of stereoisomers as determined by vpc (1% OV-1).

4-Methyl-1-(1′-propanalethylidene)-3-cyclohexene (4a, 4b). Alternate Method. 4-Isopropenyl-4-hydroxy-1-methylcyclohex-1-ene 2 (2.50 g, 22 mmol), ethyl vinyl ether (10 ml, 180 mm), mercuric acetate (6.39 g, 20 mmol) and anhydrous sodium acetate (2.46 g, 30 mmol) were sealed in a thick glass ampule under an argon atmosphere. The mixture was heated to 100° for 15 hr. The mixture was then cooled, petroleum ether (30–60°) (50 ml) was added, and the solution was washed with 5% potassium hydroxide solution (2 × 100 ml) followed by water (2 × 100 ml). The organic phase was separated and dried over anhydrous sodium carbonate and solvent evaporated. Short-path distillation of the oily residue yielded a clear sweet-smelling oil, 4-methyl-1-(1′-propanalethylidene)-3-cyclohexene, identical with the material synthesized in the two-step procedure: yield 2.10 g (82%).

γ-Bisabolene (5a, 5b). A 100-ml round-bottom 3-neck flask equipped with a magnetic stirrer, a reflux condenser, and a rubber septum was flushed with nitrogen to ensure dryness. Isopropyltriphenylphosphonium iodide[8] (669.3 mg, 1.55 mmol) was added. Dry tetrahydrofuran (5 ml) was added, and the solution was cooled to 0°. *n*-Butyllithium (0.68 ml, 1.50 mmol, 2*M*) was added dropwise to obtain an intense-red-colored solution which was stirred at 0° for 30 min. A solution of the aldehyde (267 mg, 150 mmol) in tetrahydrofuran was added. The solution was stirred at 40° for 30 min, then at room temperature for 3 hr. The mixture was poured onto ice-water and extracted with petroleum ether (30–60°). The hydrocarbon layer was washed several times with water and dried over sodium sulfate. The solvent was evaporated, yielding a clear oil (200 mg). The oil was purified by preparative thin layer chromatography on silica gel PF-254 to obtain a hydrocarbon whose spectral properties were identical to those of a commercial sample of γ-bisabolene[9]: yield 150 mg (49%); ir (CCl_4) 1680, 1460, 1380, 1240, 1180, 1160, 1120, 940 cm^{-1}; nmr (CCl_4) δ 1.56 (s, 3 H), 1.62 (s, 9 H), 2.01 (s, 6 H), 2.23 (m, 2 H), 2.68 (s, 2 H), 5.10 (t, 1 H), 5.27 (2, 1 H); high resolution mass spectrum M^+ 204.1884, $C_{15}H_{24}$ requires 204.1878. The synthetic mixture consisted of a 60:40 mixture of stereoisomers, as determined by vpc on 1% OV-1. The spectral data were in close agreement with published values.[10]

1,1,1,3,3,3-Hexadeuterio-2-propyltriphenylphosphonium Iodide (7). A solution of acetone-d_6 (20 g, 0.31 mol) in anhydrous ether (25 ml) was added dropwise to a cooled slurry of lithium aluminum hydride (6.07 g, 0.16 mol) in anhydrous ether (75 ml) and the mixture was stirred for 30 min at 0°. Dropwise addition of water (5 ml) was followed by dropwise addition of 15% sodium hydroxide solution (6 ml) and finally water (18 ml). A granular precipitate was removed by filtration and the ether extract dried over sodium sulfate.

The dried solution was added to a stirred solution of o-phenylene phosphochlorite (50.4 g, 0.29 mol) and dry pyridine (22.9 g, 0.29 mol) in ether (400 ml) at 0°. The mixture was allowed to stand for 18 hr at 25°. Pyridine hydrochloride was removed by filtration and the solvent evaporated *in vacuo* to yield an oil. Distillation of the oil gave hexadeuterioisopropyl-*o*-phenylene phosphite: yield 45 g (77%); bp 54° (1 mm); ir (film) 3100, 2250, 1600 cm^{-1}; nmr (CCl_4) δ 4.17 (d, 1 H), 7.08 (s, 4 H); high resolution mass spectrum M^+ 204.0825, $C_9H_5D_6O_3P$ requires 204.0822.

Iodine (50.4 g, 0.1 mol) was added to a solution of the phosphite (20.4 g, 0.1 mol) in dichloromethane (400 ml). The solution was stirred for 15 hr at 25° and then extracted with 5% sodium hydroxide solution (400 ml), 5% sodium bisulfite solution (200 ml), and saturated sodium chloride solution (200 ml). The dichloromethane layer was dried over anhydrous sodium sulfate and the solvent then carefully distilled at atmospheric pressure. The residue was distilled to obtain hexadeuterioisopropyl iodide: yield 13.9 g (79%); bp 88°; ir (film) 2950, 2250 cm^{-1}; nmr (CCl_4) δ 4.23 (s, 1 H). This material rapidly decomposes and was used without further purification.

The iodide (13.9 g, 79 mmol) and triphenylphosphine (20.43 g, 78 mmol) were heated together to 100°. The melt was stirred for 15 hr at 100° using an efficient reflux condenser to prevent loss of the iodide. The salt was allowed to cool and washed with petroleum ether. The crude product was recrystallized from ethanol (100%) to obtain white crystals of hexadeuterioisopropyltriphenylphosphonium iodide: yield 15.1 g (45%); mp >200° dec; nmr ($CDCl_3$) δ 4.95 (d, 1 H), 7.40 (s, 5 H), 7.85 (s, 10 H).

Hexadeuterio-γ-bisabolene (6). A 2.2 *M* solution of *n*-butyllithium in hexane (2.88 ml, 6.36 mmol) was added to a stirred solution of hexadeuterioisopropyltriphenylphosphonium iodide (2.80 g, 6.40 mmol) in tetrahydrofuran (25 ml) under an argon atmosphere at 0°. After stirring for 30 min at 0°, a solution of the aldehyde (1.13 g, 6.36 mmol) in tetrahydrofuran (20 ml) was added. The reaction was worked up according to the procedure for γ-bisabolene to obtain hexadeuterio-γ-bisabolene as a clear oil: yield 547 mg (41%); high resolution mass spectrum M^+ 210.2255 $C_{15}H_{18}D_6$ requires 210.2254.

Acknowledgments. This research was supported by a training grant (GM-01045-11) from the National Institutes of Health and by unrestricted grants from Abbott Laboratories and Hoffmann-La Roche.

Registry No.—1, 5259-65-4; **2,** 3419-02-1; **3,** 53586-54-2; **4a,** 53585-11-8; **4b,** 53585-12-9; **5a,** 53585-13-0; **5b,** 13062-00-5; **6a,** 53585-14-1; **6b,** 53586-55-3; **7,** 1787-43-5; 2-bromopropene, 557-93-7; acetone-d_6, 666-52-4; o-phenylene phosphochlorite, 1499-17-8; hexadeuterioisopropyl-o-phenylene phosphite, 53535-10-7; hexadeuterioisopropyl iodide, 39091-64-0; triphenylphosphine, 603-35-0.

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A *seco*-Germacradienolide from *Liatris pycnostachya*

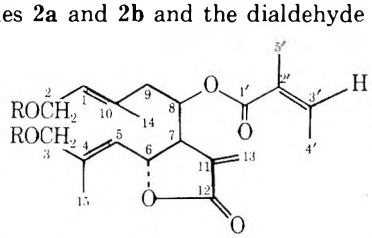
Summary: Discovery and structure determination of the first *seco*-germacradiene pycnolide, a 2,3-*seco*-1(10),4,5-germacradienolide from *Liatris pycnostachya* (Michx.) Kuntze, is reported.

Sir: Germacradienes play a crucial role in biogenetic schemes leading to many other classes of sesquiterpenes,[1] particularly those which, like the germacranes, are heavily represented in nature as sesquiterpene lactones. We now report discovery of the first *seco*-germacradiene pycnolide as a minor lactonic constituent of *Liatris pycnostachya* (Michx.) Kuntze.

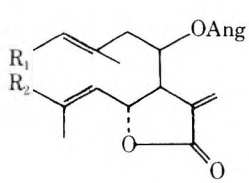
Pycnolide (**1a**), $C_{20}H_{28}O_6$[2] {$[\alpha]^{22}D$ +39.8° (c 1.1, $CHCl_3$), ir 3400, 1765, 1720 and 1650 cm^{-1}}, is an angeloyl ester (see characteristic peaks in Table I) and an α-methylene γ-lactone of the type shown in **1a** (typical signals for H-6, H-7, H-13a, and H-13b[3] whose relationship was established by spin decoupling). Other functional groups are two primary hydroxyls (AB quartet of H-2, two proton singlet of H-3, both shifted downfield on acetylation to **1b**), and two double bonds of type $-C(CH_3)=CH-$ (two additional vinyl methyls, two vinyl proton signals at 5.30 and 5.52 ppm, the latter superimposed on the signal of a proton on the carbon carrying the angelate). The remaining two nmr signals revealed the presence of a methylene group (C-9); hence pycnolide contains no ring other than that of the lactone.

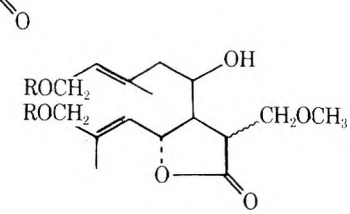
The above conclusions were corroborated by the ^{13}C nmr spectrum which exhibited the expected two carbonyl singlets (169.7, 166.8), four vinyl singlets (C-10, C-4, C-11, C-2′ at 142.7, 135.9, 132.3, 127.2), three vinyl doublets (C-3′, C-5, C-1 at 138.8, 128.9, 121.6), one vinyl triplet (C-13, 123.3), doublets of C-6 and C-8 (74.6, 71.3), triplets of C-3, C-2, and C-9 (66.3, 58.7, 41.9), doublet of C-7 (47.7), and four methyl quartets (20.3, 15.8, 15.6, 14.0).[4]

MnO_2 oxidation of **1a** gave the conjugated monoaldehydes **2a** and **2b** and the dialdehyde **2c**. The accompanying downfield shifts of H-1 (in **2a**) and H-5 (in **2b**) permitted unambiguous determination of the entire sequence C-3 through C-2 by double resonance, thus establishing the carbon skeleton as that of a 2,3-*seco*-1(10),4,5-germacradienolide. Hydrolysis of **1a** (NaOMe, MeOH, room temperature, 10–12 hr) furnished **3a** in whose nmr spectrum the H-8 multiplet, formerly at 5.52 ppm, had undergone the expected diamagnetic shift, whereas the signal near 5.3 ppm (H-6) had not been affected significantly and was still spin-coupled to H-5. Hence the lactone rings of **1a** and **3a** were closed to C-6.[6]



1a, R = H
b, R = Ac





2a. R_1 = CHO; R_2 = CH_2OH
b. R_1 = CH_2OH; R_2 = CHO
c, R_1, R_2 = CHO

3a, R = H
b, R = Ac

Table I: The 270-MHz Spectrum of Pycnolide ($CDCl_3$)[a]

H-1	5.30 tbr (6)	H-9b	2.16 dd (15, 6)
H-2	4.12 (AB)	H-13a	6.36 d (2.8)
H-3	4.06	H-13b	5.70 d (2.6)
H-5	5.52 dbr (9.5)	H-14	1.73 br[b]
H-6	5.35 dd (9.5, 5.3)	H-15	1.83 br[c]
H-7	3.10 m	H-3′	6.1 m
H-8	5.52 ddd (8.5, 6, 2)	H-4′	1.93 dq
H-9a	2.45 dd (15, 8.5)	H-5′	1.83 br

[a] Frequencies in ppm downfield from TMS. Figures in parentheses are coupling constants in Hz. [b] Coupled to H-1. [c] Coupled to H-5.

E stereochemistry around the 1,10 and 4,5 double bonds was evident, *inter alia*, from the chemical shifts of the aldehydic proton in **2b** (9.50 ppm)[7] and the C-10 methyl signal in **2a** (2.26 ppm).[8] The absolute configuration at C-8 was established as *R* by applying Horeau's method[9] to **3b** (14.2% optical yield). Since $J_{6,7}$ in **3a** and **3b** is 9 Hz, the lactone ring must be trans-fused (models). If the usual assumption is made that the C-7 side chain is β, H-6 is β as well. Thus the stereochemistry of pycnolide at C-6, C-7, and C-8 is the same as that deduced for all germacranolides and guaianolides isolated previously[10] from *Liatris* species.

It is interesting that, contrary to the situation prevailing in other classes of *seco*-terpenoids, the oxidation states of both C-2 and C-3 (or C-15[3]) of pycnolide are lower than what they must have been prior to ring cleavage.

Acknowledgment. This work was supported by grants from the U.S. Public Health Service through the National Cancer Institute (CA-13121) and Hoffmann-La Roche, Inc.

References and Notes

(1) W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev. Chem. Soc.*, **21**, 331 (1967); G. Rücker, *Angew. Chem.*, **85**, 895 (1973).
(2) Since all substances encountered in this study were difficult-to-analyze gums, composition was established by high resolution mass spectrometry and purity by tlc and ^1H and ^{13}C nmr criteria.
(3) Numbering reflects derivation from a germacradiene system. Either C-3 or C-15 of pycnolide could represent C-3 of the hypothetical germacradiene precursor.
(4) Tentative assignments on the basis of predicted chemical shifts, published information,[5] and ^{13}C nmr spectra of lactones of known structure in our files.
(5) N. S. Bhacca, F. W. Wehrli, and N. H. Fischer, *J. Org. Chem.*, **38**, 3618 (1973); N. S. Bhacca, R. A. Wiley, N. H. Fischer, and F. W. Wehrli, *J. Chem. Soc., Chem. Commun.*, 615 (1973).
(6) The relatively simple fragmentation of **1a** and its derivatives under electron impact is fully consonant with structure **1a** and will be discussed in our full publication.
(7) *E.g.*, K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968); A. F. Thomas and M. Ozainne, *Chem. Commun.*, 47 (1969); U. Schwieter and S. Liaaen-Jensen, *Acta Chem. Scand.*, **23**, 1057 (1969).
(8) *E.g.*, P. B. Venuto and A. R. Day, *J. Org. Chem.*, **29**, 2735 (1964); K. T. Suzuki, N. Suzuki, and S. Nozoe, *Chem. Commun.*, 527 (1971).
(9) A. Horeau, *Tetrahedron Lett.*, 506 (1961); 965 (1962); A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964); W. Herz and H. B. Kagan, *J. Org. Chem.*, **32**, 216 (1967).
(10) S. M. Kupchan, V. H. Davis, T. Fujita, M. R. Cox, R. J. Restivo, and R. F. Bryan, *J. Org. Chem.*, **38**, 1853 (1973); W. Herz and I. Wahlberg, *Phytochemistry*, **13**, 1421 (1973); W. Herz and I. Wahlberg, *J. Org. Chem.*, **38**, 2485 (1973); W. Herz, J. Poplawski, and R. P. Sharma, *J. Org. Chem.*, **40**, 199 (1975); W. Herz and R. P. Sharma, *Phytochemistry*, in press.

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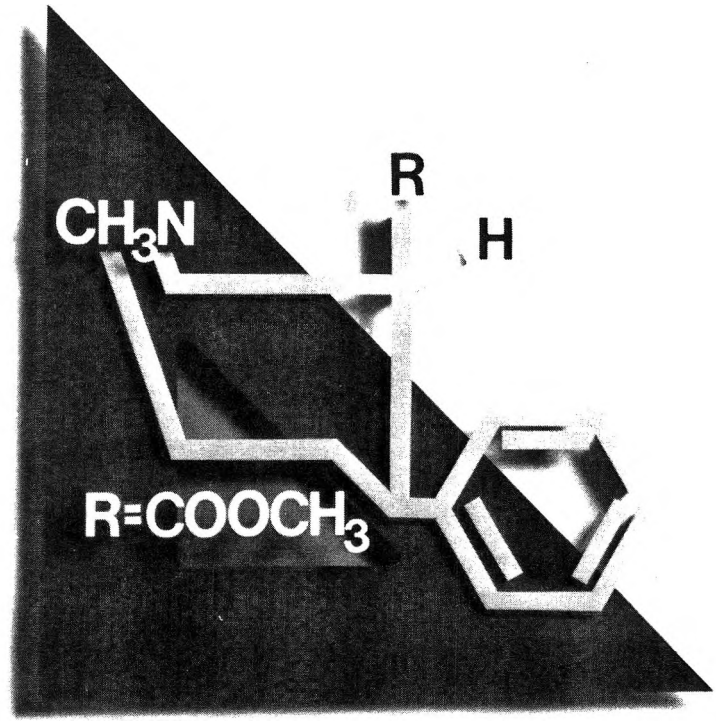
Drug Design



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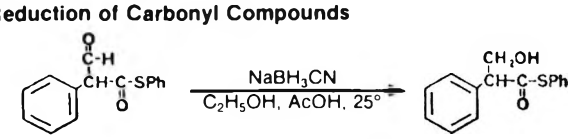
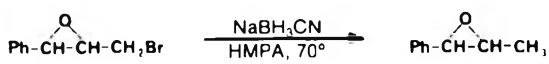
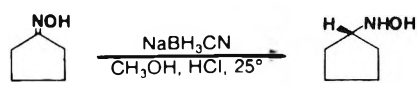


Reductive Displacement of Halides

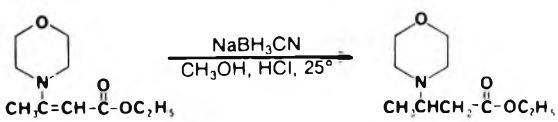


The most useful application of $NaBH_3CN$ is the selective reduction of the iminium ion ($>C=\overset{+}{N}<$). The following are some specific reductions, all of which involve an intermediate iminium ion.

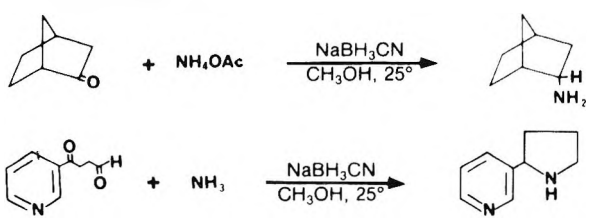
Reduction of Oximes

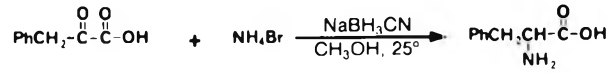


Reduction of Enamines

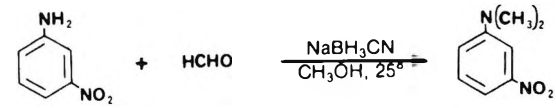


Reductive Amination

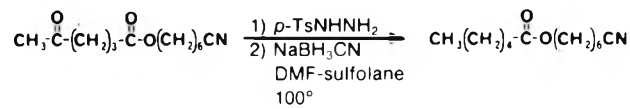




Reductive Alkylation



Deoxygenation (Modified Wolff-Kishner)



The stability and reactivity of the cyanoborohydride ion in aqueous systems at pH 6-8 indicate the potential for carrying out imine reductions and carbonyl aminations on complex biological systems. For example, the imino linkage between 11-*cis*-retinal and the lipoprotein, opsin, was recently reduced with $NaBH_3CN$ under mild conditions (aqueous, pH 5, 3°).

For a complete list of references, please send for a detailed technical information bulletin. The following are leading references:

R.F. Borch, M.D. Bernstein, and H.D. Durst, *J. Amer. Chem. Soc.*, **93**, 2897 (1971).

R.O. Hutchins and D. Kandasamy, *ibid.*, **95**, 6131 (1973); and references cited therein.

C.F. Lane, *Synthesis*, 1975, in press.

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