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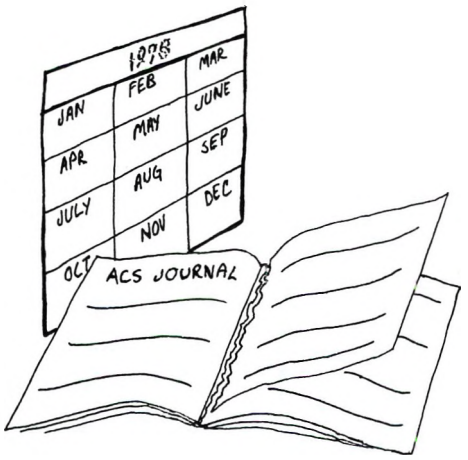

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AUTHOR INDEX

THE JOURNAL OF Organic Chemistry

VOLUME 41, NUMBER 16

AUGUST 6, 1976

Pentacyclic Triterpene Synthesis. 5. Synthesis of Optically Pure Ring AB Precursors[1]

John S. Dutcher, James G. Macmillan, and Clayton H. Heathcock*

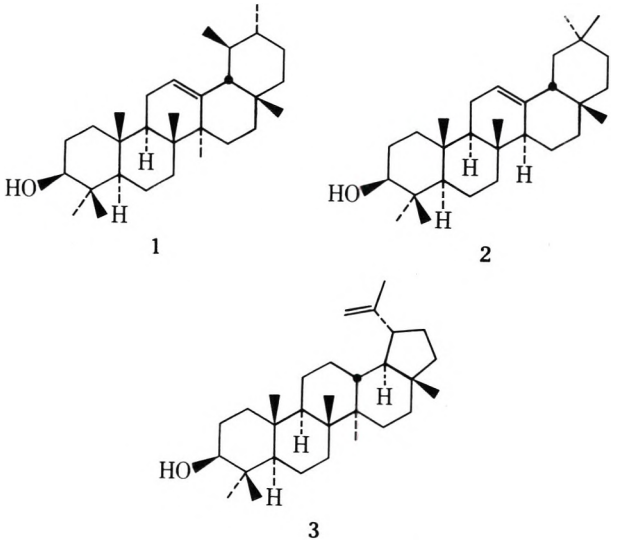
Department of Chemistry, University of California, Berkeley, California 94720

Received December 22, 1975

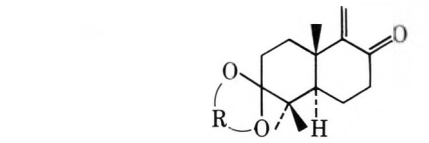
Bicyclic enone **5**, which is a precursor for rings A and B of the pentacyclic triterpenes, has been synthesized in ten steps from enedione **14** in 16% overall yield. Unsaturated keto alcohol **15** has been resolved into its enantiomers and absolute stereostructures assigned. The levorotatory enantiomer of **5** has the absolute configuration corresponding to that of the pentacyclic triterpenes.

In contrast to the massive amount of research which has been directed toward the total synthesis of the lower terpenes and steroids,[2] relatively little attention has been paid to triterpenes.[3] This lack of interest has been due in part to the fact that the triterpenes are relatively devoid of interesting physiological activity, and in part to their greater complexity. Within the triterpene class,[4] the pentacyclic group is the most numerous and represents the greatest structural complexity. The most notable synthetic achievements to date are Stork's synthesis of lupeol,[5] Ireland's syntheses of alnusenone[6] and shionone,[7] Ireland and Johnson's synthesis of germanicol,[8] van Tamelen's synthesis of tetrahymanol,[9] and Prestwick and Labovitz's synthesis of serratenediol.[10] In addition, van Tamelen has reported a biogenetic synthesis involving cyclization of a bicyclic polyolefinic epoxide which affords a mixture of δ-amyrin, β-amyrin, and germanicol.[11]

In most of the pentacyclic triterpenes, rings A and B are the same; the differences occur mainly in rings C, D, and E, as illustrated below with α-amyrin (**1**), β-amyrin (**2**), and lupeol (**3**). We have initiated a convergent synthetic approach in which preformed AB and DE synthons would be coupled together, and then ring C would be closed. In such an approach, the same AB synthon might serve for the synthesis of a variety of the triterpenes. Our candidate for a general AB synthon is the bicyclic enone **5**. In this paper, we report the synthesis, in racemic form, of enones **4** and **5**, and in optically pure form of enone **5**.



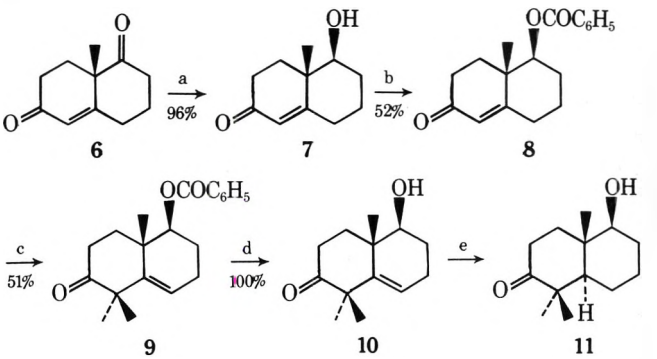
1 **2** **3**



4, R = $-CH_2CH_2-$
5, R = $-CH_2C(CH_3)_2CH_2-$

As a precursor to enones **4** and **5**, we chose keto alcohol **11**, which had previously been prepared by Sondheimer and Elad (Chart I).[12] However, in our hands, this route to **11** proved exceptionally tedious. In particular, the hydrogenation of **10** to **11** is erratic. Unless **10** is scrupulously purified (column chromatography), diol **12** is a major product of the hydroge-

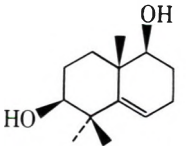
Chart I



6 **7** **8** **9** **10** **11**

a, $NaBH_4$, EtOH; b, C_6H_5COCl, pyridine; c, *t*-BuOK, CH_3I; d, KOH, EtOH; e, H_2, Pd/C, EtOH.

nation. Even when **10** is carefully purified, the reduction is slow and large amounts of catalyst are required (50–100 weight percent), and some cis keto alcohol **13** is often obtained.



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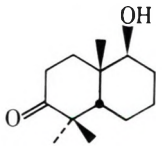

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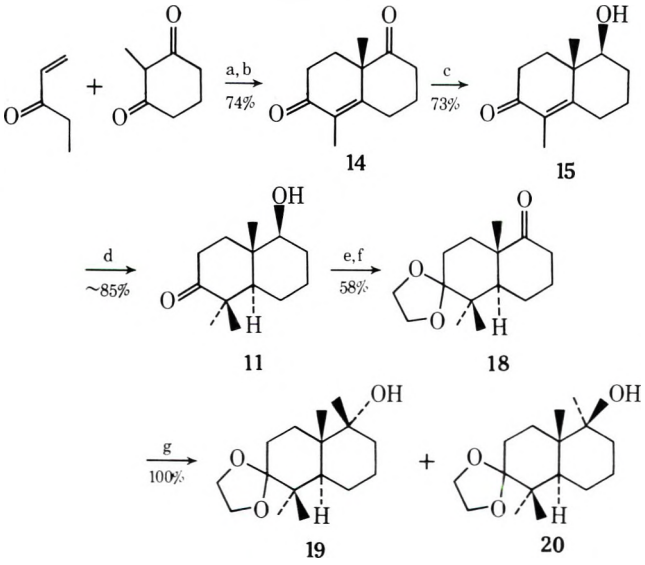
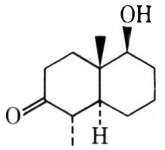
To circumvent these problems, we developed an alternate synthesis of **11**, which is both shorter and more reliable (Chart II).[13] Dimethyloctalindione **14** is produced by Robinson an-

Chart II



a, KOH, CH_3OH; b, pyrrolidine, benzene; c, $NaBH_4$, EtOH; d, Li, NH_3, CH_3I; e, $HOCH_2CH_2OH$, β-$NpSO_3H$, benzene; f, bispyridinechromium(VI) oxide, CH_2Cl_2; g, CH_3Li, ether.

nelation of 2-methyl-1,3-cyclohexanedione with ethyl vinyl ketone. Selective reduction of the saturated carbonyl in **14** affords the crystalline keto alcohol **15** in 73% yield. Reductive methylation of **15** by a modification of Stork's procedure[14] affords keto alcohol **11**, along with about 8% of the reduced, unalkylated keto alcohol **16** and 8% of dialkylated keto alcohol



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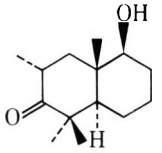

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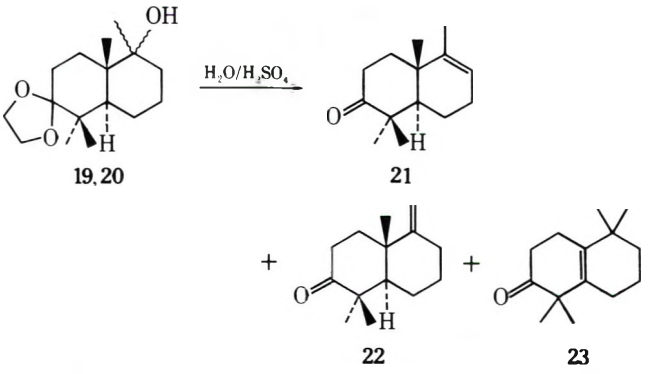
17. Ketalization of the crude product from reductive methylation affords a crystalline hydroxy ketal, which is oxidized to ketone **18**. This ketone reacts with methyllithium in ether at −78 °C to give a 3:2 mixture of tertiary alcohols **19** and **20**.

The stereochemistry of the tertiary carbinol center in alcohols **19** and **20** was assigned using the NMR shift reagent tris(2,2,6,6-tetramethylheptane-3,5-dionato)europium(III).[15] Upon addition of shift reagent, the resonance due to the angular methyl group shifted downfield much more for the minor isomer (**20**) than for the major isomer (**19**).[16]

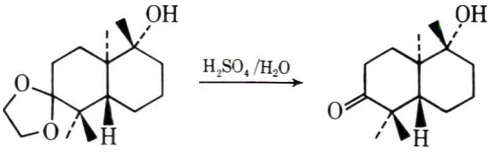
Acid-catalyzed dehydration of the mixture of **19** and **20** (aqueous H_2SO_4/pentane or CCl_4, heterogeneous) affords a mixture of olefins **21**, **22**, and **23**. The amount of exocyclic olefin **22** and rearranged olefin **23** produced was found to be



19, **20** **21** **22** **23**

dependent on the concentration of acid used in the dehydration and upon the organic solvent used as second phase. Results are tabulated in Table I. For dehydration of the racemic mixture of **19** and **20**, 25% H_2SO_4/H_2O proved to be optimal. Using stronger acid gave more rearranged product, and also caused subsequent rearrangement of **21** to **22**. For example, after 1 h using 50% H_2SO_4/H_2O, the ratio of **23** to **21** had increased to 73:27. However, with more dilute acid, the initial dehydration product is unchanged even after much longer reaction times.

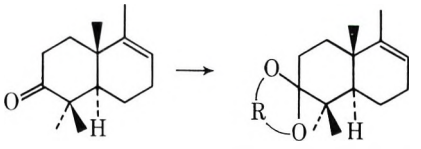
A practical problem arose when we attempted the aqueous H_2SO_4/pentane dehydration of enantiomerically pure samples of **19** and **20** (vide infra). For example, attempted dehydration of the 4a*R* alcohol **20a** in this system resulted in the rapid



20a **24**

precipitation of keto alcohol **24**. Because of its low solubility in pentane, no dehydration occurred. For the optically active series, CCl_4 was found to be a suitable organic phase, the optimum acid strength being 35% (Table I).

Ketalization of the crude dehydration product, followed by crystallization, gave pure ketals **25** or **26** in 54–58% yield, based on alcohols **19**–**20**.



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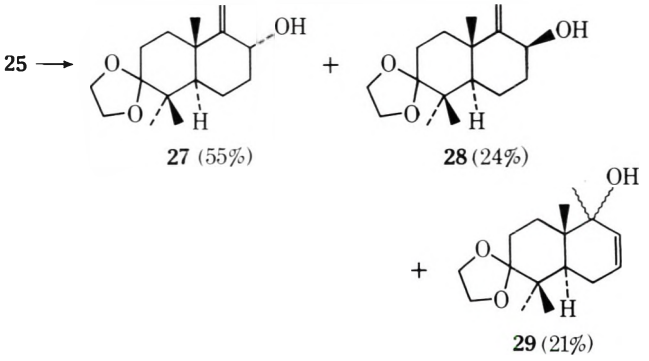
25, R = $-CH_2CH_2-$
26, R = $-CH_2C(CH_3)_2CH_2-$

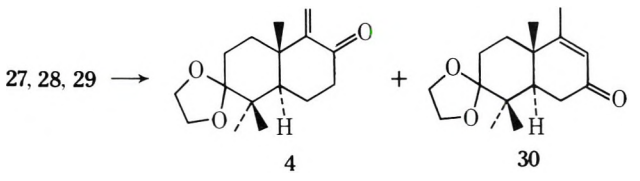
We completed the synthesis of enones **4** and **5** by two methods. Initially, we examined the reaction of olefin **25** with singlet oxygen. Oxygenation of **25** using rose bengal as sensitizer gave a mixture of allylic alcohols **27**–**29** in the ratio indicated. Alcohols **27** and **28** were separated and their stere-



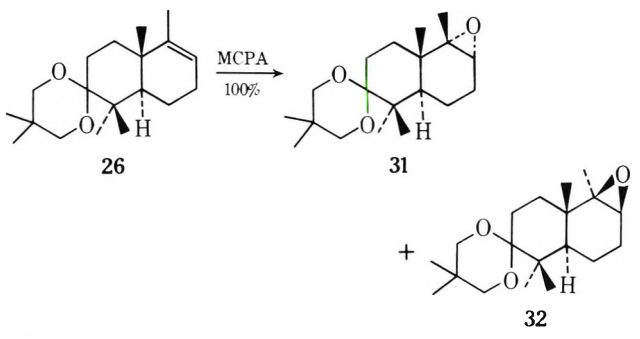
27 (55%) **28** (24%) **29** (21%)

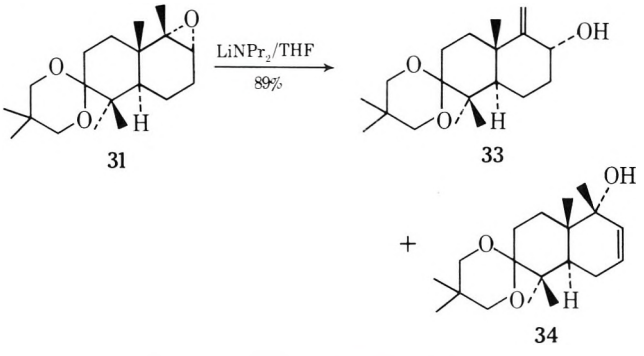
ostructures were assigned on the basis of their NMR spectra. The carbinol proton resonances in **27** and **28** have half-height bandwidths ($W_{1/2}$) of 21 and 5 Hz, respectively. Thus, the hydroxyl group in **27** is equatorial, while that in **28** is axial.[17]

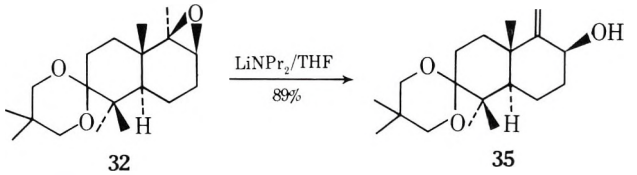
Oxidation of the mixture of **27, 28,** and **29** with bispyridinechromium(VI) oxide in methylene chloride[18] affords a mixture of enones **4** and **30** in a ratio of 3:1. After chromatography, the enones were isolated in yields of 39 and 13%, respectively, based on olefin **25.** The oxidation of tertiary allylic alcohol **29** to enone **30,** which involves allylic rearrangement of the intermediate chromate ester, is well precedented.[19]



Alternatively, olefin **26** may be epoxidized by *m*-chloroperoxybenzoic acid to an equimolar mixture of epoxides **31** and **32.** Samples of the two pure epoxides were obtained by fractional crystallization in order to study the base-catalyzed ring-opening reaction. Epoxide **31** reacted with lithium di-*n*-propylamide in refluxing THF[20] for 4 h to give a 3:2 mixture of alcohols **33** and **34** in 94% yield. Epoxide **32** reacted more slowly under these conditions, requiring 6 h for completion, but gave only isomer **35** in 89% yield. As in the case of alcohols **27** and **28,** stereostructures were assigned to alcohols **33** and **35** on the basis of the half-height bandwidths of the carbinol resonances ($W_{1/2}$ = 21 and 5 Hz, respectively).





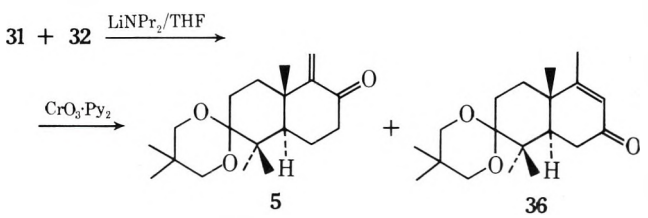


When the crude mixture of epoxides **31** and **32** is treated with lithium di-*n*-propylamide, and the resulting mixture of alcohols oxidized with bispyridinechromium(VI) oxide, enones **5** and **36** are obtained in a ratio of 71:29. After chromatography, enone **5** is obtained in 58% yield, based on olefin **26.** Thus, the most efficient route to enone **5** (**14** → **15** → **11** → **18** → **19** + **20** → **21** → **26** → **31** + **32** → **33** + **35** → **5**) requires ten steps and affords **5** in 16% overall yield.

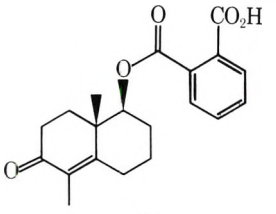
Table I. Dehydration of Alcohols 19 and 20

Acid concn,[a] %	Organic phase	Reaction time, min[b]	Product analysis, % 21	22	23
50	Pentane	5	44	0	56
30	Pentane	90	88	4	8
25	Pentane	420	89	6	5
20	Pentane	60	No dehydration		
50	CCl_4	30	76	0	24
40	CCl_4	150	88	3	9
35	CCl_4	450	87	5	8
30	CCl_4	180	No dehydration		

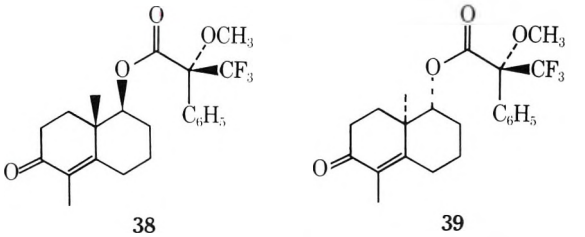
[a] Volume/volume H_2SO_4/H_2O in aqueous phase. [b] Reactions were followed to complete disappearance of starting material by GLC. Time cited is for complete reaction.



Unsaturated keto alcohol **15** was converted to the hydrogen phthalate **37,** which was resolved via the brucine salt. A pure dextrorotatory salt was obtained after four recrystallizations from acetone. Careful acidification of this salt afforded (+)-**37** ([α]D 176.2°), which was hydrolyzed with 5 N aqueous KOH (see Experimental Section) to afford (+)-**15** ([α]D +162.7°). The mother liquors from recrystallization of the brucine salt of **37** were acidified to obtain levorotatory **37.** After recrystallization, (−)-**37** ([α]D −171.6°) was obtained. Alkaline hydrolysis of this material afforded (−)-**15** ([α]D −164.4°). Overall yields for the resolution were 31% for (+)-**15** and 28% for (−)-**15.** It is interesting that racemic **15** is a crystalline solid with mp 88–89 °C, and the pure enantiomers are liquids at room temperature.



Optical purities for the resolved alcohols were determined by Mosher's method,[21] using the (+)-α-methoxy-α-trifluoromethylphenylacetyl esters **38** and **39.** Analysis was accomplished with the methoxy ^1H NMR resonances (δ 3.44 and 3.37 ppm for isomers **38** and **39,** respectively) and the CF_3 ^{19}F NMR resonances (−7.65 and −7.49 ppm from trifluoroacetic acid for isomers **38** and **39,** respectively. Both enantiomers were found to be ≥94% optically pure.[22]



Absolute stereostructures were assigned to (+)-**15** and (−)-**15** on the basis of their circular dichroism spectra. The dextrorotatory enone shows a strong positive $\pi \rightarrow \pi^*$ Cotton effect and a weak negative $n \rightarrow \pi^*$ Cotton effect.[23] On the basis of analogy to similar enones of known structure,[24] (+)-**15** may therefore be assigned the (4a*S*,5*S*) configuration.

Optically pure (−)-**15** ([α]D −164.4°) has been converted, by the sequence of reactions discussed earlier in the paper, into optically pure enone (+)-**5** ([α]D +66.9°) via (+)-**18** ([α]D +51.8°) and (−)-**26** ([α]D −14.3°). Thus, the levorotatory enantiomer of enone **5** ([α]D −67°) has the absolute configuration corresponding to that of the pentacyclic triterpenes.

Experimental Section

Melting points (Pyrex capillary) are uncorrected. The following instrumentation was used to record spectra: infrared (ir), Perkin-Elmer 137 and 237; ultraviolet (uv), Perkin-Elmer 202; mass spectra, Varian MS-12; high-resolution mass spectra, Consolidated 21-110B; optical rotations, Carl Zeiss polarimeter; circular dichroism (CD), Cary Model 60; proton magnetic resonance (^{1}H NMR), Varian T-60. The line positions for the ^{1}H NMR spectra are given in the δ scale as parts per million downfield from internal trimethylsilane. Significant ^{1}H NMR data are tabulated in the order (number of protons, multiplicity, proton assignments). Gas–liquid partition chromatography (GLC) analyses were performed on a Varian Aerograph 90-P instrument. Brinkmann Silplates (PSF-22, 0.5 mm thickness, 20 × 20 cm) were used for preparative thin layer chromatography (preparative TLC). Elemental analysis were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, Calif.

(±)-1,4a-Dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5-(3*H*,6*H*)-dione (14). A solution of 73.1 g (0.58 mol) of methyldihydroresorcinol,[25] 75.3 g (0.90 mol) of ethyl vinyl ketone, and 225 ml of methanol was made basic with potassium hydroxide pellets and then refluxed for 4 h. The solvent and excess ethyl vinyl ketone were removed on a rotary evaporator at room temperature, using benzene as an azeotroping agent.

The yellow residue was dissolved in 380 ml of benzene, and 5.6 ml (65 mmol) of pyrrolidine was added. After refluxing the solution for 16 h with water separation (Dean-Stark trap), it was cooled, washed with 5% hydrochloric acid, water, and saturated brine, dried ($MgSO_4$), and evaporated. The light-red oil (117 g) was distilled to give 82.3 g (74%) of yellow oil, bp 133–160 °C (0.4 Torr). Crystallization from ethyl acetate/hexane gave the analytical sample: mp 46.0–47.5 °C; ir (CCl_4) 1701, 1650, 1590, 1447, 1437, 1346, 1323, 1304, 1235, 1106, 1007 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.42 ppm (3 H, s, angular CH_3), 1.72 ppm (3 H, s, vinyl CH_3).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.85; H, 8.20.

(±)-1,4aβ-Dimethyl-5β-hydroxy-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (15). A solution of 1.05 g (0.11 equiv) of sodium borohydride in 240 ml of absolute ethanol was added over 3 h to a stirring solution of 20.0 g (0.10 mol) of **14** and 120 ml of absolute ethanol cooled in an ice bath. After an additional 20 min the excess hydride was destroyed by slowly adding 2.2 ml of acetic acid. The solvent was evaporated and the residue was taken up in chloroform. After washing with water and drying over $MgSO_4$, the solvent was evaporated to give 23.8 g of yellow oil which crystallized upon standing. Recrystallization from hexane/acetone gave 14.8 g (73.4%) of white crystals, mp 86–89 °C. A second recrystallization gave the analytical sample: mp 88–89 °C; ir (CCl_4) 3480, 1680, 1600, 1000 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.14 (3 H, s, angular CH_3), 1.70 (3 H, s, vinyl CH_3).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.89; H, 9.31.

(±)-1,4aβ-Dimethyl-5β-hydroxy-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one Hydrogen Phthalate (37). A mixture of 1.00 g (5.15 mmol) of (±)-**15**, 0.79 g (5.30 mmol) of phthalic anhydride, and 1.9 ml of pyridine was stirred under nitrogen for 68 h. The solution was then poured into ice and 10% hydrochloric acid, and the white precipitate removed by filtration and recrystallized from acetone to afford 1.45 g (82.5%) of white solid: mp 186–189 °C; ir ($CDCl_3$) 1706, 1656, 1351, 1299, 943 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.28 (3 H, s, angular CH_3), 1.80 (3 H, s, vinyl CH_3), 4.86 (1 H, m, C-5 H).

Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 69.99; H, 6.34.

Resolution of 37. To a solution of 24.0 g (70.2 mmol) of (±)-**37** dissolved in 400 ml of boiling acetone was added 27.6 g (70.0 mmol) of brucine hydrate dissolved in 100 ml of acetone. The solvent volume was reduced to 150 ml and the solution refrigerated to induce crystallization. The solid which formed was isolated and then recrystallized to constant rotation (twice more): [α]^{25}D +18.8° (c 4.00, $CHCl_3$).

A solution of 21.0 g (28.6 mmol) of the dextrorotatory brucine salt dissolved in 300 ml of acetone was poured with rapid stirring into 600 ml of ice and water containing 25 ml of 5% hydrochloric acid. After 1 h, the solid was removed by filtration and dried. Crystallization from acetone to constant rotation gave 8.99 g (76% from (±)-**37** based on one enantiomer) of crystals: mp 190–192.5 °C; [α]^{25}D +172.6 ° (c 2.01, $CHCl_3$).

To a magnetically stirred suspension of 8.8 g (25.7 mmol) of (+)-**37**, 50 ml of water, and 50 ml of ether cooled to 5 °C was slowly added 50 ml of 40% potassium hydroxide. The reaction flask was fitted with a continuous extractor and magnesium sulfate was added to the receiving flask (to precipitate any base dissolved in the ether during the extraction). The ice bath was removed and the solution was extracted with ether for 24 h. The organic solution was filtered and evaporated to give 5.2 g (100%) of (+)-**15** as a yellow oil: [α]^{25}D +162.6° (c 2.17, $CHCl_3$); uv (MeOH) λ_{max} 250 nm (ε 14,740); CD (MeOH) [θ] 37 100 (247 nm), −5500 (319 nm).[23]

The mother liquors from the resolution were combined and stripped of solvent to give a brownish semisolid. A solution of 2.97 g (4.04 mmol) of this salt dissolved in 15 ml of acetone was treated as described for the salt of the dextrorotatory acid to give 1.28 g (68% from (±)-**37**, based on one enantiomer) of white solid: mp 190.5 °C; [α]^{25}D −174.5° (c 2.02, $CHCl_3$). This acid (8.1 g, 24.7 mmol) was hydrolyzed as described previously to yield 4.8 g (100%) of (−)-**15** as a yellow oil: [α]^{25}D −164.6° (c 2.16, $CHCl_3$); uv (MeOH) λ_{max} 250 nm (ε 12 850), 309 (81); CD (MeOH) [θ] −24 800 (247 nm), +4780 (320 nm).[23]

1,4aβ-Dimethyl-5β-hydroxy-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one α-Methoxy-α-trifluoromethylphenylacetate (38 and 39). Into a 10 × 75 mm oven-dried test tube fitted with a rubber septum were syringed the following compounds: 300 μl of anhydrous pyridine, 45 mg (30 μl, 0.18 mmol) of (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride[21] dissolved in 150 μl of carbon tetrachloride, and 21 mg (0.11 mmol) of (±)-**15** dissolved in 150 μl of carbon tetrachloride. The tube was shaken and allowed to stand at room temperature for 2 h, after which 100 μl of 3-dimethylamino-1-propylamine was added. After 5 min, the solution was diluted with 10 ml of ether, washed with cold 5% hydrochloric acid, cold 5% sodium bicarbonate, and saturated brine, dried ($MgSO_4$), and evaporated. The procedure was repeated using samples of (+)-**15** and (−)-**15**.

The ^{1}H NMR spectra of each of the three ester samples were measured at 60 MHz for ^{1}H and at 56.4 MHz for ^{19}F. The relevant shifts and assignments for compounds **38** (+,+ ester) and **39** (−,+ ester) are summarized in Table II. The ester produced from (±)-**15** was found to be a mixture of 63% **38** and 37% **39**, indicating that (+)-**15** undergoes esterification more rapidly than (−)-**15**. The esters produced from (+)-**15** and (−)-**15** were found to have the following diastereomeric composition (% **38**, % **39**): (+)-**15** (96.2, 3.8); (−)-**15** (12.6, 87.4). These crude values were corrected for the greater reactivity of (+)-**15** to obtain enantiomeric purities of the resolved alcohols of ≥94% each.

5β-Hydroxy-1,1,4aβ-trimethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3H)-one (11). An apparatus consisting of a three-necked flask, a dry ice condenser, and a pressure-equalizing dropping funnel was oven dried and assembled, along with a magnetic stirrer and a nitrogen bubbler. Liquid ammonia (700 ml) was distilled from lithium into the flask immersed in a dry ice/isopropyl alcohol bath. Lithium wire (1.37 g, 196.0 mmol) was added, the bath was removed, and stirring was continued for 0.5 h. A solution of 10.0 g (5.15 mmol) of **15** in 100 ml of anhydrous THF was added dropwise over 0.5 h. After another 0.5 h, 50 ml (540 mmol) of methyl iodide was added as rapidly as possible. Violent reaction was observed until the blue color was discharged. One minute after addition was complete the white heterogeneous mixture turned clear and lithium iodide slowly precipitated. After 15 min, solid ammonium chloride was added, the condenser was replaced with a water-cooled condenser, and 300 ml of ether was added. The ammonia was evaporated, the residue washed with 5% hydrochloric acid, and the acid washings extracted with ether. The combined organic solutions were washed with 5% sodium bicarbonate and saturated brine, dried ($MgSO_4$), and evaporated to give 10.8 g (100%) of yellow, viscous oil: ir (CCl_4) 3356, 1701, 1449, 1385, 1366, 1248, 1149, 1057, 862 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.00 (2 × 3 H, s), 1.03 (3 H, s). Mass spectral analysis indicated that little (less than 10%) reduced or trimethylated ketone was present. Several attempts were made to remove these impurities, but all were unsuccessful.

Recrystallization from hexane afforded a crystalline product (mp 54.5–60 °C) which still contained approximately 8% each of hydroxy ketones **16** and **17**.

5β-Hydroxy-1,1,4aβ(*S*)-trimethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one [(4a*S*)-11]. Keto alcohol (+)-**15** (5.6 g, 28.9 mmol) was reduced as described above to afford 6.1 g (100%) of yellow oil.

5β-Hydroxy-1,1,4aβ(*R*)-trimethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one [(4a*R*)-11]. Keto alcohol (−)-**15** (8.3 g, 42.8 mmol) was reduced as described above to afford 9.1 g (100%) of yellow oil.

1,4aβ-Dimethyl-5β-hydroxy-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one (16). Liquid ammonia (60 ml) was distilled from lithium into a flame-dried apparatus consisting of a 100-ml three-necked flask fitted with a dry ice condenser, a nitrogen bubbler, a magnetic stirrer, and a pressure-equalizing dropping funnel. Lithium wire (77 mg, 2.14 mmol) was added, the blue solution was stirred for 0.5 h, and a solution of 1.0 g (5.2 mmol) of **15** in 10 ml of anhydrous THF was slowly added. Another 41 mg (16.9 mmol total) of lithium wire was needed to maintain the blue color during the addition. Thirty minutes after the addition was complete, excess ammonium chloride was added and the ammonia allowed to evaporate overnight. The residue was partitioned between water and ether, the layers separated, and the aqueous phase extracted with ether. The combined organic solutions were dried ($MgSO_4$) and evaporated to give 0.99 g (98%) of slightly yellow oil which crystallized upon standing. The analytical sample was obtained by recrystallization from hexane: mp 83–84.5 °C; ir (KBr pellet) 3990, 1709, 1447, 1058 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (3 H, d, J = 7 Hz, C-1 CH_3), 1.07 (3 H, s, angular CH_3), 3.22 (1 H, m, C-5 H).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.41; H, 10.08.

5β-Hydroxy-1,1,4aβ-trimethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one Ethylene Ketal. A stirring solution of 18.2 g (92.2 mmol) of **11**, 50 ml (895 mmol) of ethylene glycol, 1.0 g of β-naphthalenesulfonic acid, and 500 ml of benzene was refluxed for 68 h with water separation (Soxhlet extractor containing calcium hydride). The yellow solution was washed with 5% sodium bicarbonate, water, and saturated brine, dried ($MgSO_4$), and evaporated to give 23.5 g (99.6%) of white-orange solid. Recrystallization from hexane gave the analytical sample: mp 101.5–102.5 °C; ir (CCl_4) 1247, 1087, 868 cm^{-1}; ^1H NMR (CCl_4) δ 0.77 (3 H, s), 0.87 (3 H, s), 0.90 (3 H, s), 3.06 (1 H, m, C-5 H), 3.83 (4 H, s, ketal H's).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.02; H, 10.19.

5β-Hydroxy-1,1,4aβ(*S*)-trimethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one Ethylene Ketal. Crude keto alcohol (4a*S*)-**11** (6.42 g, 30.6 mmol) was ketalized as described above. After 36 h of reflux, 7.8 g (100%) of yellow solid was isolated.

5β-Hydroxy-1,1,4aβ(*R*)-trimethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one Ethylene Ketal. Crude keto alcohol (4a*R*)-**11** (5.2 g, 24.8 mmol) was ketalized as described above. After 53 h of reflux, 6.3 g (100%) of yellow solid was isolated.

1,1,4aβ-Trimethyl-1,4,4a,7,8,8aα-hexahydronapthalene-2,5(3*H*,6*H*)-dione 2-Ethylene Ketal (18). To a mechanically stirred solution of 90 ml (1.1 mol) of pyridine (distilled from barium oxide) and 1.4 l. of methylene chloride (distilled from phosphorus pentoxide) cooled in ice was added 56 g (0.56 mol) of chromium trioxide (stored over phosphorus pentoxide). The burgundy solution was stirred for 30 min, and then 23.5 g (92.5 mmol) of ketal alcohol dissolved in 100 ml of methylene chloride was added in one portion. After another 15 min, the dark mixture was vacuum filtered through Woelm alumina (activity 4). A small amount of methylene chloride was used to rinse the flask and the alumina. The clear organic solutions were evaporated to give a greenish solid which was recrystallized from hexane to give 13.5 g (57.9% from **11**) of white crystals: mp 121–122 °C; ir (CCl_4) 1709, 1248, 1112, 1103, 909, 865 cm^{-1}; ^1H NMR (CCl_4) δ 0.83 (3 H, s), 1.00 (3 H, s), 1.50 (3 H, s), 3.92 (4 H, s, ketal H's).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.16; H, 9.58.

(−)-1,1,4aβ(*S*)-Trimethyl-1,4,4a,7,8,8aα-hexahydronaphthalene-2,5(3*H*,6*H*)-dione 2-Ethylene Ketal [(−)-18]. Crude (4a*S*)-ketal alcohol (11.0 g, 43.4 mmol) was oxidized as described in the preceding procedure. Recrystallization from hexane to constant rotation gave 6.2 g [57.6% from (+)-**15**] of white needles: mp 108–112 °C; $[\alpha]^{24}D$ −53.9° (*c* 2.08, $CHCl_3$).

(+)-1,1,4aβ(*R*)-Trimethyl-1,4,4a,7,8,8aα-hexahydronaphthalene-2,5(3*H*,6*H*)-dione 2-Ethylene Ketal [(+)-18]. Crude (4a*R*)-ketal alcohol (9.6 g, 37.9 mmol) was oxidized as described in the preceding procedure. Recrystallization from hexane to constant rotation gave 5.7 g [50.6% from (−)-**15**] of white needles: mp 105–114 °C; $[\alpha]^{25}D$ +51.8° (*c* 2.00, $CHCl_3$).

Table II. Chemical Shifts for Compounds 38 and 39

Ester	^1H NMR[a] Angular CH_3	Vinyl CH_3	OCH_3	5α-H	^{19}F NMR,[b] CF_3
38	73	104	212	287	−7.65
39	74	104	208	285	−7.49

[a] ^1H NMR shifts given in hertz downfield from internal Me_4Si at 60 MHz. [b] ^{19}F NMR shifts given in parts per million downfield from external trifluoroacetic acid.

5α-Hydroxy-1,1,4aβ,5β-Tetramethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one Ethylene Ketal (19) and 5β-Hydroxy-1,1,4aβ,5α-tetramethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one Ethylene Ketal (20). Methyllithium (1.5 M in ether, 20 ml, 30 mmol) was added to a dry three-necked flask fitted with a nitrogen bubbler, a pressure-equalizing dropping funnel, and a magnetic stirrer. After the solution was cooled in a dry ice/isopropyl alcohol bath, a solution of 1.96 g (7.8 mmol) of **18** in 100 ml of anhydrous ether was added dropwise over 3 h. After 45 min of stirring at room temperature, 50 ml of 5% ammonium chloride was added, the layers were separated and the aqueous phase was extracted with ether. The combined organic solutions were washed with saturated brine, dried ($MgSO_4$), and evaporated to give 2.1 g (100%) of a light yellow oil which solidified upon standing, mp 72–94 °C.

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.33; H, 10.35.

Addition of $Eu(THD)_3$ shift reagent to the solid split the ketal proton ^1H NMR absorptions into two groups, indicating a 3:2 mixture of the two possible isomeric alcohols. Four recrystallizations of the alcohol mixture from hexane gave white crystals: mp 106–111 °C; ir (CCl_4) 3460, 1198, 1138, 1112, 1093 cm^{-1}; ^1H NMR (CCl_4) δ 0.80 (3 H, s), 0.90 (3 H, s), 0.98 (3 H, s), 1.03 (3 H, s), 3.84 (4 H, s, ketal H's). The mother liquors from the first recrystallization were concentrated and another crop of crystals was obtained. Recrystallization three times from hexane gave white crystals: mp 92–98 °C; ir (CCl_4) 1458, 1387, 1370, 1142, 1093 cm^{-1}; ^1H NMR (CCl_4) δ 0.82 (3 H, s), 0.93 (3 H, s), 1.03 (3 H, s), 1.25 (3 H, s), 3.85 (4 H, s, ketal H's).

Each of the separated alcohols was dissolved in carbon tetrachloride, and ^1H NMR spectra were determined after the addition of varying amounts of $Eu(THD)_3$. The chemical shifts of the four methyl resonances and the ketal resonance of each isomer was plotted against the amount of $Eu(THD)_3$ per milligram of each isomer. As expected, the C-5 methyl shifted substantially in both isomers, and the ketal resonance was relatively unaffected in each isomer. Of the remaining three methyl resonances, two were relatively unaffected in each isomer (probably the C-1 methyls). The chief difference occurred in the methyl resonance at δ 1.25 ppm in the minor isomer. This resonance shifted to δ 6 ppm after the addition of 0.8 mg of $Eu(THD)_3$ per milligram of alcohol. Consequently, we assign structure **20** to this isomer.[16]

The methyllithium addition was repeated on enantiomerically pure (+)-**18** and (−)-**18**, giving quantitative yields of the corresponding alcohols (4a*R*)-**19** + **20** and (4a*S*)-**19** + **20**, respectively.

1,1,4aβ,5-Tetramethyl-1,4,4a,7,8,8aα-hexahydronaphthalen-2(3*H*)-one (21). To a stirring solution of 15.7 g (56.8 mmol) of **19** + **20** and 320 ml of pentane was added 320 ml of 30% (volume/volume) sulfuric acid. After 12 h, the organic layer was washed with 5% sodium bicarbonate and satrated brine, dried ($MgSO_4$), and evaporated to afford 11.0 g (85%) of yellow oil. ^1H NMR and GLC analysis indicated a 88:4:8 mixture of **21**, **22**, and **23**. Preparative GLC gave the analytical samples.

Olefin **21**: ir (neat) 1706, 1458, 1381, 1112 cm^{-1}; ^1H NMR (CCl_4) δ 1.05 (3 H, s), 1.07 (3 H, s), 1.10 (3 H, s), 1.63 (3 H, d, $J \approx 2$ Hz, C-5 CH_3), 5.23 (1 H, m, C-6 H).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.27; H, 10.72.

Olefin **23**: ir (neat) 1715, 1460, 1374, 1355, 1094, 955 cm^{-1}; ^1H NMR (CCl_4) δ 1.03 (6 H, s), 1.10 (6 H, s).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.38; H, 10.57.

1,1,4aβ(*S*),5-Tetramethyl-1,4,4a,7,8,8aα-hexahydronaphthalen-2(3*H*)-one [(4a*S*)-21]. The foregoing dehydration procedure was repeated using 8.3 g (31.0 mmol) of (4a*S*)-**19** + **20**, 165 ml of carbon tetrachloride, and 165 ml of 35% (volume/volume) sulfuric acid. After 6.75 h, workup gave 6.8 g (100%) of yellow oil. ^1H NMR and GLC

analysis showed a 84:6:10 mixture of (4a*S*)-**21**, (4a*S*)-**22**, and (4a*S*)-**23**.

1,1,4aβ(*R*),5-Tetramethyl-1,4,4a,7,8,8aα-hexahydronaphthalen-2(3*H*)-one [(4a*R*)-21]. Alcohols (4a*R*)-**19** + **20** (6.2 g, 23.1 mmol) were treated as described above to give 4.7 g (99%) of yellow oil. ^{1}H NMR and GLC analysis showed the product to be a 87:5:8 mixture of (4a*R*)-**21**, (4a*R*)-**22**, and (4a*R*)-**23**.

1,1,4aβ,5-Tetramethyl-1,4,4a,7,8,8aα-hexahydronaphthalen-2(3*H*)-one Ethylene Ketal (25). A solution of 54 mg (2.6 mmol) of crude **21**, 1.5 ml (22 mmol) of ethylene glycol, 50 ml of anhydrous benzene, and a trace of β-naphthalenesulfonic acid was stirred and refluxed for 46 h with water separation (Soxhlet extractor containing calcium hydride). The solution was washed with 5% sodium bicarbonate and water, dried ($MgSO_4$), and evaporated to give 62 mg of slightly yellow solid. Recrystallization from methanol gave 35 mg (54% from **18**) of white crystals: mp 107–108 °C; ir (CCl_4) 2882, 1383, 1106, 1095, 1054 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.82 (3 H, s), 0.92 (3 H, s), 1.02 (3 H, s), 1.48 (3 H, s), 3.87 (4 H, s, ketal H's), 5.01 (1 H, m, C-6 H).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.61; H, 10.30.

1,1,4aβ,5-Tetramethyl-1,4,4a,7,8,8aα-hexahydronaphthalen-2(3*H*)-one 2,2-Dimethyltrimethylene Ketal (26). Crude **21** (11.0 g, 51 mmol) was ketalized as described above, using 27.8 g (267 mmol) of 2,2-dimethyl-1,3-propanediol in place of the ethylene glycol. Workup gave 16.6 g of yellowish solid which was recrystallized from methanol to afford 9.9 g (58% from **18**) of fine, white crystals: mp 112–113 °C; ir (CCl_4) 1244, 1106, 1095, 862, 842 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.65 (3 H, s), 0.77 (3 H, s), 0.95 (6 H, s), 1.10 (3 H, s), 3.33 (4 H, complex m, ketal H's), 4.98 (1 H, m, C-6 H).

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.84; H, 10.97.

1,1,4aβ(*R*),5-Tetramethyl-1,4,4a,7,8,8aα-hexahydronaphthalen-2(3*H*)-one 2,2-Dimethyltrimethylene Ketal [(−)-26]. Crude (4a*R*)-**21** (5.8 g, 26.8 mmol) was ketalized as described above to give 8.2 g of yellow solid. Recrystallization from hexane to constant rotation yielded 4.65 g [56.8% from (+)-**18**] of long needles: mp 124–126 °C; $[\alpha]^{25}$D −14.3° (*c* 2.12, $CHCl_3$).

(+)-1,1,4aβ(*S*),5-Tetramethyl-1,4,4a,7,8,8aα-hexahydronaphthalen-2(3*H*)-one 2,2-Dimethyltrimethylene Ketal [(+)-26]. Crude (4a*S*)-**21** (6.8 g, 32.9 mmol) was ketalized as described above to give 8.7 g of yellow solid. Recrystallization from hexane to constant rotation yielded 5.4 g [63.0% from (−)-**18**] of fine, white needles: mp 123–125 °C; $[\alpha]^{25}$D +14.7° (*c* 4.14, $CHCl_3$).

5-Methylene-1,1,4aβ-trimethyl-1,4,4a,5,8,8aα-hexahydronaphthalene-2,6(3*H*,7*H*)-dione 2-Ethylene Ketal (4) and 1,1,4aβ,5-Tetramethyl-1,4,4a,8aα-tetrahydronaphthalene-2,7(3*H*,8*H*)-dione 2-Ethylene Ketal (30). A solution of 1.7 g (6.7 mmol) of **25**, 100 ml of isopropyl alcohol, and 340 mg of rose bengal was placed in an immersion-type photoreactor. Oxygen was bubbled through the deep-red solution while it was photolyzed with a 450-W Hanovia lamp through a Pyrex filter. Analysis (TLC) of the reaction mixture showed only a small amount of starting material after 7 h. Irradiation was continued for an additional 0.5 h, and the alcohol solution was then stirred overnight with 3 g of potassium iodide. The dark mixture was evaporated and the residue taken up in ether, washed with water and 10% sodium thiosulfate, dried ($MgSO_4$), and evaporated. ^{1}H NMR analysis of the yellow oil (1.6 g, 88.8%) showed the product to be a mixture of 55% of **27**, 24% of **28**, and 21% of **29**.

Anhydrous chromium trioxide (3.6 g, 36 mmol) was added under nitrogen to a magnetically stirred solution of 5.8 ml (72 mmol) of anhydrous pyridine and 90 ml of anhydrous methylene chloride. After 20 min, 1.57 g (5.9 mmol) of the foregoing mixutre of **27**, **28**, and **29** dissolved in methylene chloride was added in one portion. After 20 min, the solution was vacuum filtered through Woelm alumina (activity 4) and the clear solution evaporated to give 1.33 g of oil. Column chromatography (60 g silica gel, 40% ether/hexane) gave two compounds.

The early fractions afforded 690 mg (39.4% from **25**) of enone **4**: ir (CCl_4) 2950, 1669, 1623, 1381, 1105, 907, 863 cm^{-1}; uv (MeOH) λ_{max} 227 nm (ϵ 4100); ^{1}H NMR (CCl_4) δ 0.88 (3 H, s), 1.00 (3 H, s), 1.07 (3 H, s), 3.90 (4 H, broad s, ketal H's), 4.91 (1 H, d, J = 2 Hz, vinyl H), 5.10 (1 H, d, J = 2 Hz, vinyl H).

The later fractions yielded 230 mg of enone **30**: ir (CCl_4) 2967, 1706, 1623, 1381, 1282, 1199, 1107, 911, 865 cm^{-1}; uv (MeOH) λ_{max} 239 nm (ϵ 11 800); ^{1}H NMR (CCl_4) δ 0.85 (3 H, s), 1.02 (3 H, s), 1.15 (3 H, s), 2.22 (3 H, s, vinyl CH_3), 3.92 (4 H, broad s, ketal H's), 3.59 (1 H, broad s, vinyl H).

5β,6β-Oxido-1,1,4aβ,5α-Tetramethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one 2,2-Dimethyltrimethylene Ketal (32) and 5α,6α-Oxido-1,1,4aβ,5β-tetramethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one 2,2-Dimethyltrimethylene Ketal (31). To a stirring solution of 5.0 g (17.1 mmol) of **26** and 150 ml of chloroform was added 5.6 g (26.9 mmol) of *m*-chloroperoxybenzoic acid. After 2 h, the solution was washed with 10% potassium hydroxide, dried ($MgSO_4$), and evaporated to give 5.3 g (100%) of white crystals, mp 93–128 °C. ^{1}H NMR analysis showed this product to be a mixture of epoxides, with a slight excess (5%) of the β isomer (**32**). Repeated crystallization from hexane gave β-epoxide **32** as white needles: mp 145.5–146.4 °C; ir (CCl_4) 1129, 1116, 1095, 1037, 1027, 899 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.72 (3 H, s), 0.78 (3 H, s), 0.97 (3 H, s), 1.02 (3 H, s), 1.12 (3 H, s), 1.17 (3 H, s), 2.72 (1 H, broad s, $W_{1/2}$ = 4 Hz), 3.33 (4 H, complex m, ketal H's).

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.93; H, 10.30.

Recrystallization of the mother liquors from above did not give pure α-epoxide **31**. Dissolution in hexane and slow evaporation (over several days) gave two types of crystals: needles (β-epoxide) and rectangles (α-epoxide). These were manually separated and the procedure repeated on the α-epoxide to afford **31** as rectangular crystals: mp 123.5–126 °C; ir (CCl_4) 1129, 1116, 1104, 910, 864 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.72 (3 H, s), 0.78 (3 H, s), 0.93 (3 H, s), 1.05 (3 H, s), 1.12 (3 H, s), 1.15 (3 H, s), 2.66 (1 H, broad s, $W_{1/2}$ = 6 Hz, epoxide H), 3.35 (4 H, complex m, ketal H's).

Anal. Calcd for $C_{19}H_{32}O_3$: mol wt, 308.2352. Found: 308.2339 (high-resolution mass spectrum).

5,6-Oxido-1,1,4aβ(*R*),5-tetramethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one 2,2-Dimethyltrimethylene Ketal [(4a*R*)-31 and (4a*R*)-32]. Olefin (−)-**26** (4.5 g, 15.4 mmol) was epoxidized as described above to afford 4.7 g (100%) of α- and β-epoxides (4a*R*)-**31** and (4a*R*)-**32**.

6α-Hydroxy-5-methylene-1,1,4aβ-trimethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one 2,2-Dimethyltrimethylene Ketal (33) and 5α-Hydroxy-1,1,4aβ,5β-tetramethyl-1,4,4a,5,8,8aα-hexahydronaphthalen-2(3*H*)-one 2,2-Dimethyltrimethylene Ketal (34). To an oven-dried three-necked flask and a reflux condenser fitted with a magnetic stirrer, a rubber septum, and a nitrogen bubbler were added 124 mg (1.2 mmol) of di-*n*-propylamine (distilled from potassium hydroxide), 0.9 ml of anhydrous THF, and 0.83 ml (1.5 M in hexane, 1.2 mmol) of *n*-butyllithium. After 30 min, a solution of 252 mg (0.82 mmol) of epoxide **31** and 1.7 ml of THF were added and the mixture brought to reflux. The disappearance of epoxide was followed by TLC. After 2 h, the solution was partitioned between ether and water and the organic solution washed with water and saturated brine, dried ($MgSO_4$), and evaporated. ^{1}H NMR analysis of the yellow, oily product (243 mg, 96.2%) showed it to be a mixture of 60.5% of **33** and 39.5% of **34**. Careful chromatography of this product (silica gel, 5% ether/hexane) separated the two compounds. The first material eluted from the column was identified as **34**, a white solid: ^{1}H NMR (CCl_4) δ 0.70 (3 H, s), 0.87 (3 H, s), 0.93 (3 H, s), 0.98 (3 H, s), 1.03 (3 H, s), 1.13 (3 H, s), 3.42 (4 H, complex m, ketal H's), 5.35 (2 H, complex m, vinyl H's).

Anal. Calcd for $C_{19}H_{32}O_3$: mol wt, 308.2352. Found: 308.2343 (high-resolution mass spectrum).

The second material eluted was identified as allylic alcohol **33**, which was also obtained as a white solid: mp 128–129 °C; ir (CCl_4) 3636, 2959, 1650, 1383, 1244, 1107, 1045, 1027, 898, 865 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.73 (3 H, s), 0.85 (3 H, s), 0.98 (3 H, s), 1.07 (3 H, s), 1.17 (3 H, s), 3.48 (4 H, complex m, ketal H's), 4.16 (1 H, broad m, $W_{1/2}$ = 21 Hz, C-6 H), 4.62 (1 H, broad s, vinyl H), 4.68 (1 H, broad s, vinyl H).

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.90; H, 10.49.

6β-Hydroxy-5-methylene-1,1,4aβ-trimethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3*H*)-one 2,2-Dimethyltrimethylene Ketal (35). Epoxide **32** (300 mg, 0.97 mmol) was treated for 4.5 h as described for **31** above. The oily product contained 7% of starting material.

Chromatography (14 g of silica gel, 30% ether/hexane) gave 270 mg (96.3% based on recovered starting material) of oil which crystallized upon standing. Recrystallization from hexane gave the analytical sample: mp 103.5–105 °C; ir (CCl_4) 3571, 2941, 1634, 1111, 1033, 1010, 912, 863 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.73 (3 H, s), 0.88 (3 H, s), 0.98 (3 H, s), 1.17 (3 H, s), 1.25 (3 H, s), 3.48 (4 H, complex m, ketal H's), 4.20 (1 H, broad s, $W_{1/2}$ = 6 Hz, C-5 H), 4.66 (1 H, broad s, vinyl H), 4.73 (1 H, broad s, vinyl H).

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.71; H, 10.37.

When the lithium di-*n*-propylamide ring-opening reaction was carried out on an equimolar mixture of α- and β-epoxides **31** and **32**, a mixture of 73% of **33** and **35** and 27% of **34** was obtained.

5-Methylene-1,1,4aβ-trimethyl-1,4,4a,5,8,8aα-hexahydronaphthalene-2,6(3*H*,7*H*)-dione 2-(2,2-Dimethyl)trimethylene Ketal (5) and 1,1,4aβ,5-Tetramethyl-1,4,4a,8aα-tetrahydronaphthalene-2,7(3*H*,8*H*)-dione 2-(2,2-Dimethyl)trimethylene Ketal (36). To a stirring solution of 6.5 ml (81 mmol) of anhydrous pyridine and 80 ml of anhydrous methylene chloride was added 3.2 g (32 mmol) of dry chromium trioxide. After 15 min, 1.7 g (5.5 mmol) of a mixture of **33, 34,** and **35,** obtained from opening of an equimolar mixture of **31** and **32,** dissolved in a small amount of methylene chloride, was added in one portion. After 15 min, the dark solution was vacuum filtered through activity 4 Woelm alumina, and the organic solution was evaporated to afford 1.08 g of yellow solid. ^{1}H NMR analysis indicated a mixture of 71% of **5** and 29% of **36.** Chromatography (40 g of silica gel, 20% ether/hexane) yielded two fractions.

The first fraction (0.99 g, 58% from 26) was shown to be enone **5.** Recrystallization from hexane gave the analytical sample: mp 118–122 °C; ir ($CDCl_3$) 1692, 1618, 1381, 1285, 1212, 1129, 1106, 1027 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.74 (3 H, s), 0.93 (3 H, s), 1.03 (3 H, s), 1.08 (3 H, s), 1.15 (3 H, s), 3.35 (4 H, complex m, ketal H's), 4.72 (1 H, d, J = 1 Hz, vinyl H), 5.25 (1 H, d, J = 1 Hz, vinyl H).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.38. Found: C, 74.39; H, 9.59.

The second fraction was identified as **36.** Recrystallization from ether gave the analytical sample: mp 189–189.5 °C; ir ($CDCl_3$) 1658, 1626, 1244, 1105 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.73 (3 H, s), 0.98 (3 H, s), 1.05 (3 H, s), 1.15 (3 H, s), 1.20 (3 H, s), 2.34 (3 H, s, vinyl CH_3), 3.50 (4 H, complex m, ketal H's), 5.69 (1 H, broad s, vinyl H).

(+)-5-Methylene-1,1,4aβ(*R*)-trimethyl-1,4,4a,5,8,8aα-hexahydronaphthalene-2,6(3*H*,7*H*)-dione 2-(2,2-Dimethyl)trimethylene Ketal [(+)-5]. The foregoing procedure was repeated with 2.4 g of a mixture of α- and β-epoxides obtained from (−)-**26.** The product allylic alcohol mixture (2.4 g, 7.3 mmol) was oxidized as described above to obtain 1.40 g [59.5% based on (−)-**26**] of (+)-**5** as a white powder, mp 148–152 °C. Recrystallization from hexane to constant rotation gave 0.99 g [42% from (−)-**26**] of fine white crystals: mp 154.5–158 °C; $[\alpha]^{25}$D +66.9° (c 8.00, $CHCl_3$).

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Registry No.—**4,** 59270-02-9; **5,** 52782-57-7; (+)-**5,** 59331-17-8; **11,** 52782-49-7; 11 ethylene ketal, 59331-18-9; 4a*S*-**11** ethylene ketal, 25826-86-2; 4a*R*-**11** ethylene ketal, 59331-19-0; **14,** 41019-71-0; **15,** 24138-10-1; (+)-**15,** 38405-15-1; (−)-**15,** 52842-07-6; **16,** 15292-92-9; **17,** 59286-41-8; **18,** 59270-03-0; (+)-**18,** 59331-20-3; (−)-**18,** 59331-21-4; **9,** 59270-04-1; **20,** 59331-22-5; **21,** 59270-05-2; 4a*S*-**21,** 59331-23-6; 4a*R*-**21,** 59331-24-7; **23,** 52782-59-9; **25,** 59270-06-3; **26,** 52782-51-1; (+)-**26,** 59331-25-8; (−)-**26,** 59331-26-9; **30,** 59270-07-4; **31,** 52842-10-1; **32,** 52782-54-4; **33,** 52842-11-2; **34,** 52782-56-6; **35,** 52782-55-5; **36,** 52782-58-8; **37,** 52782-39-5; (+)-**37,** 59270-08-5; (−)-**37,** 52842-06-5; (+)-**37** brucine salt, 59270-09-6; (−)-**37** brucine salt, 59270-10-9; (+,+)-**38,** 52782-40-8; (−,+)-**39,** 52782-41-9; methyldihydroresorcinol, 1193-55-1; ethyl vinyl ketone, 1629-58-9; phthalic anhydride, 85-44-9; (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride, 39637-99-5; ethylene glycol, 107-21-1; 2,2-dimethyl-1,3-propanediol, 126-30-7.

Supplementary Material Available. Circular dichroism curves for (+)-**15** and (−)-**15** and graphs of the chemical shifts of various ^{1}H NMR resonances as a function of added $Eu(THD)_3$ for alcohols **19** and **20** (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) A portion of this work has appeared in preliminary form: (a) J. S. Dutcher, J. G. Macmillan, and C. H. Heathcock, *Tetrahedron Lett.*, 929 (1974); (b) J. S. Dutcher and C. H. Heathcock, *ibid.*, 933 (1974).

(2) (a) A. F. Thomas, C. H. Heathcock, and D. Taub in "The Total Synthesis of Natural Products", Vol. II, J. W. ApSimon, Ed., Wiley, New York, N.Y., 1973; (b) A. A. Akhrem and Yu. A. Titov, "Total Steroid Synthesis", Plenum Press, New York, N.Y., 1970.

(3) J. W. ApSimon and J. W. Hooper in ref 2a.

(4) For a complete tabulation of known triterpenes, see T. K. Devon and A. I. Scott, "Handbook of Naturally-Occurring Compounds", Vol. II, Academic Press, New York, N.Y., 1972.

(5) G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, and J. Labovitz, *J. Am. Chem. Soc.*, **93,** 4945 (1971).

(6) (a) R. E. Ireland, D. A. Evans, D. Glover, R. M. Rubottom, and H. Young, *J. Org. Chem.*, **34,** 3717 (1969); (b) R. E. Ireland, M. I. Dawson, S. C. Welch, A. Hagenbach, J. Bordner, and B. Trus, *J. Am. Chem. Soc.*, **95,** 7829 (1973); (c) R. E. Ireland, P. Bey, K.-F. Cheng, R. J. Czarny, J.-F. Moser, and R. I. Trust, *J. Org. Chem.*, **40,** 1000 (1975).

(7) R. E. Ireland, C. J. Kowalski, J. W. Tilley, and D. M. Walba, *J. Org. Chem.*, **40,** 990 (1975).

(8) R. E. Ireland, S. W. Baldwin, D. J. Dawson, M. I. Dawson, J. E. Dolfini, J. Newbould, W. S. Johnson, M. Brown, R. J. Crawford, P. F. Hudrlik, G. H. Rasmussen, and K. K. Schmiegel, *J. Am. Chem. Soc.*, **92,** 5743 (1970).

(9) E. E. van Tamelen, R. A. Holton, R. E. Hopla, and W. E. Konz, *J. Am. Chem. Soc.*, **94,** 8228 (1972).

(10) G. D. Prestwick and J. N. Labovitz, *J. Am. Chem. Soc.*, **96,** 7103 (1974)

(11) E. E. van Tamelen, M. P. Seiler, and W. Wierenga, *J. Am. Chem. Soc.*, **94,** 8229 (1972).

(12) F. Sondheimer and D. Elad, *J. Am. Chem. Soc.*, **80,** 1967 (1958).

(13) The structures used in this paper are all in one enantiomeric series. All compounds are racemic unless otherwise specified in the text.

(14) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87,** 275 (1965).

(15) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Am. Chem. Soc.*, **92,** 5734 (1970).

(16) Charts showing the chemical shift for the ketal hydrogens and all methyl groups for both isomers as a function of added $Eu(THD)_3$ will appear following this paper in the microfilm edition. See paragraph at end of paper regarding supplementary material.

(17) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 79.

(18) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35,** 4000 (1970).

(19) (a) G. Büchi and B. Egger, *J. Org. Chem.*, **36,** 2021 (1971); (b) P. M. McCurry, Jr., and R. K. Singh, *ibid.*, **39,** 2316 (1974).

(20) B. Rickborn and R. P. Thummel, *J. Org. Chem.*, **34,** 3583 (1969).

(21) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Am. Chem. Soc.*, **91,** 2543 (1969).

(22) Esters **38** and **39** were prepared from the corresponding alcohols by treatment of the alcohol with (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride in CCl_4 at 25 °C for 2 h. Racemic **15** gives a 63:37 mixture of diastereomers **38** and **39** under these conditions, indicating a substantial asymmetric induction in the esterification reaction. This differential reactivity must be used to correct the crude diastereomeric ratios obtained from the resolved samples of **15** (see Experimental Section). These results emphasize the importance of performing a control reaction on the racemic alcohol when using this method to determine enantiomeric purity.

(23) The CD spectra of (+)-**15** and (−)-**15** will appear following this paper in the microfilm edition. See paragraph at end of paper regarding supplementary material.

(24) (a) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78,** 6362 (1956); (b) V. Prelog and W. Acklin, *Helv. Chim. Acta*, **39,** 748 (1956); (c) C. Djerassi, J. Osiecki, and W. Herz, *J. Org. Chem.*, **22,** 1361 (1957); (d) L. Velluz and M. Legrand, *Angew. Chem., Int. Ed. Engl.*, **4,** 840 (1965).

(25) A. B. Mekler, S. Ramachandran, S. Swaminathan, and M. S. Newman, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 743.

Pentacyclic Triterpene Synthesis. 6. Synthesis of a Bicyclic Intermediate Corresponding to Rings D and E of β-Amyrin[1]

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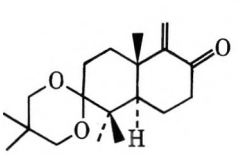
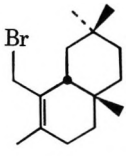
Bicyclic allylic bromide **2**, a viable synthon for rings D and E of the pentacyclic triterpenes of the germanicane class, has been synthesized.

In the preceding paper, we reported the synthesis of optically pure enone **1**, a potentially useful synthon for rings A and B in a general convergent synthesis of pentacyclic triterpenes.[2] In this paper, we report the synthesis of allylic bromide **2**, a synthon for rings D and E of β-amyrin.



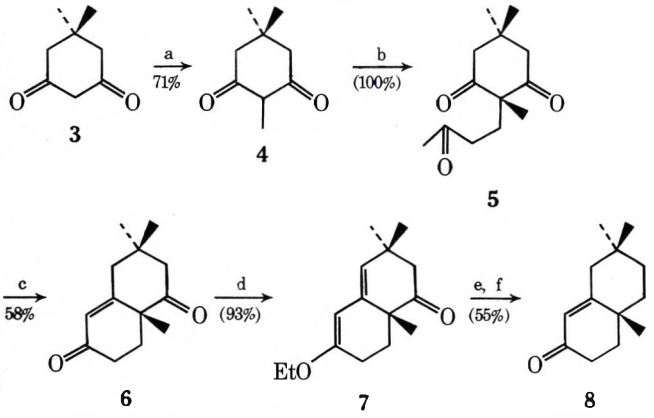
1



2

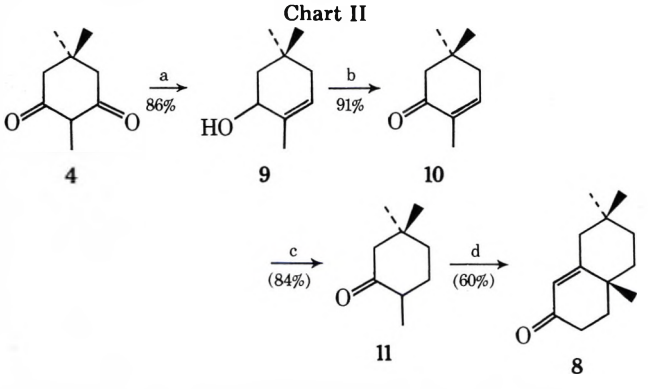
Initially, we chose octalone **8**, previously prepared by Halsall,[3] as a convenient starting material for the preparation of **2**. As the Halsall method for the preparation of 8 proved inconvenient on a large scale, we explored alternative methods for its synthesis. Our first synthesis of this material is outlined in Chart I. By this route, octalone 8 is available from dimedone (**3**) in 21% overall yield. Subsequently, we developed the more convenient method summarized in Chart II. Compound 8 is obtained from 3 in substantially higher overall yield by this route (28%), which also proved to be much more adaptable to large-scale synthesis.

Chart I



a, NaOH, CH_3I, H_2O;[4] b, $CH_3COCH{=}CH_2$, C_2H_5OH, KOH; c, *p*-TsOH, C_6H_6 —H_2O; d, $CH(OEt)_3$, C_6H_6, HCl; e, N_2H_4, $(HOCH_2CH_2)_2O$, KOH; f, dioxane, H_2O, H_2SO_4.

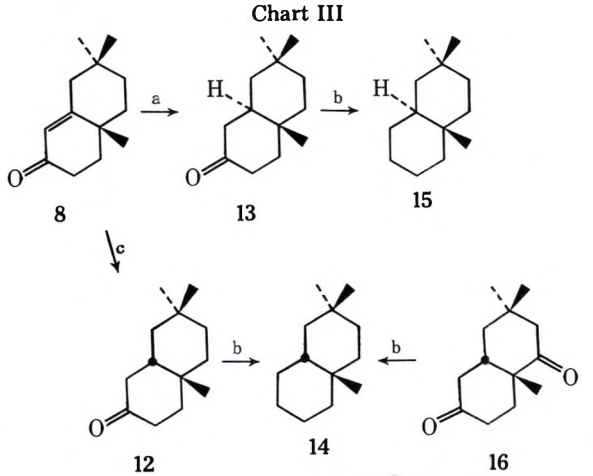
Chart II



a, $LiAlH_4$, ether; b, H_2CrO_4, C_6H_6, H_2O; c, H_2, Pd/C; d, $CH_3COCH{=}CH_2$, C_6H_6, H_2SO_4.[5]

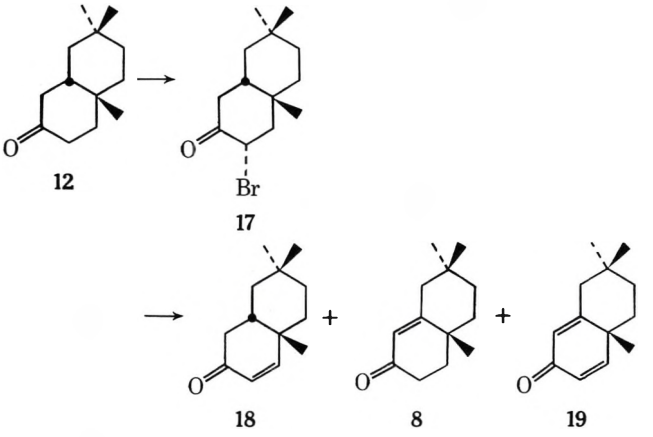
Halsall had previously reported that hydrogenation of 8 leads exclusively to the *cis*-decalone **12**.[3] However, as this assignment appears to have been made purely on analogy to similar hydrogenations of steroid enones, we carried out a more rigorous stereochemical proof (Chart III). Enone 8 was reduced catalytically (Pd/C in ethyl acetate or ethanol) and by lithium in ammonia. The products, saturated ketones **12** and **13**, were reduced by the Wolff–Kishner method to give trimethyldecalins **14** and **15**, which are readily separable by capillary GLC. Wolff–Kishner reduction of dione **16**, of known cis stereochemistry,[6] also affords isomer **14**, thus establishing the cis stereochemistry of decalone **12**.

Chart III



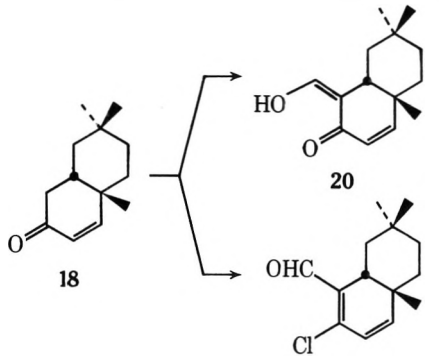
a, Li, NH_3; b, N_2H_4, $(HOCH_2CH_2)_2O$, KOH; c, H_2/Pd.

Since decalone **12** undergoes preferential enolization toward C-3,[3] it is necessary to block this position in order to functionalize C-1. Bromination of **12** yields bromo ketone **17** in quantitative yield. Dehydrobromination of **17**, with calcium carbonate in refluxing dimethylacetamide, yielded enone **18**,



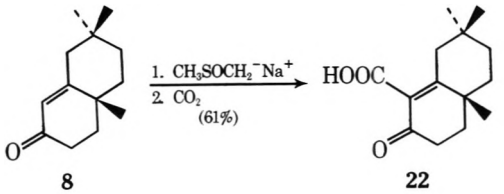
contaminated with 10–20% of enone 8 and a trace of dienone 19 (probably arising from a trace of a dibromo ketone).

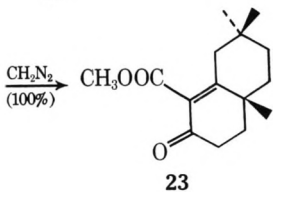
Unfortunately, enone 18 proved intractable in all attempts to functionalize C-1. Attempted reaction of 18 with sodium hydride and dimethyl carbonate under a variety of conditions led only to recovered enone. Reaction of 18 with ethyl formate and sodium ethoxide gave a complex mixture. In addition to unreacted starting enone, we were able to isolate β-keto aldehyde 20 as an impure material in rather low yield. Vilsmeier addition (phosphoryl chloride, dimethylformamide, trichloroethylene) on 18 gave chloro aldehyde 21 in about 20% yield,



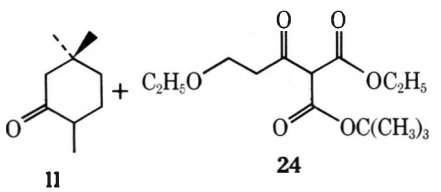
but this yield could not be improved by numerous modifications.

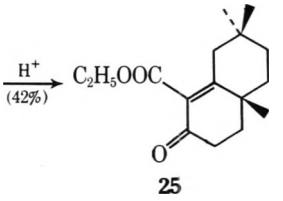
With these difficulties, we turned to direct functionalization of C-1 in enone 8. Carbonation of the anion produced in the reaction of enone 8 with methylsulfinylmethylide in dimethyl sulfoxide gives keto acid 22 in 61% yield. Diazomethane esterification of 22 affords methyl ester 23 in quantitative yield.





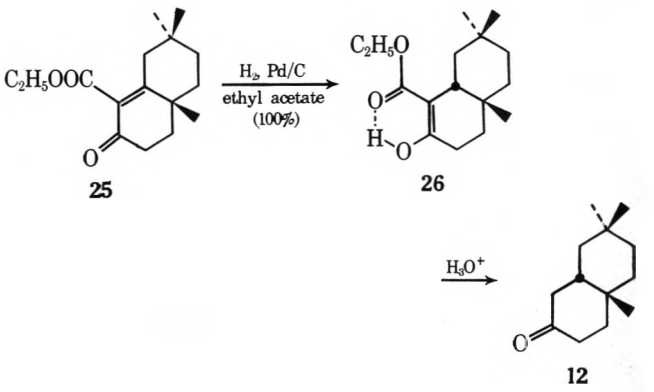
An alternative preparation of keto ester 25 involves an adaptation of the Nazarov annelation.[1b] Reaction of 2,5,5-trimethylcyclohexanone (11) with keto diester 24 in refluxing benzene with a catalytic quantity of H_2SO_4 yields β-keto ester 25 in 42% yield. The overall yields of β-keto esters 23 or 25 by the foregoing routes are comparable (37% and 42% from 2,5,5-trimethylcyclohexanone). Although the latter method





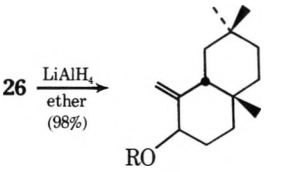
gives a higher yield of keto ester 25, the annelation reaction requires an extended reaction time.[7] On the other hand, the preparation of keto ester 23 requires the use of diazomethane for esterification.[8]

Catalytic hydrogenation of 25 (Pd/C in ethyl acetate) yields the crystalline β-keto ester 26, shown to be a single stereoisomer by hydrolysis and decarboxylation to *cis*-decalone 12.

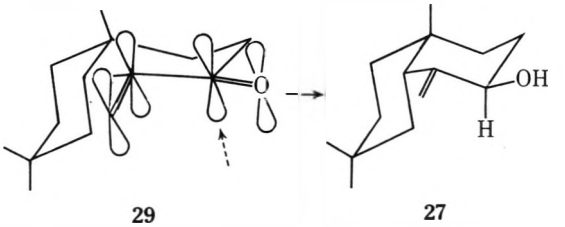


Compound 26 apparently exists totally in the chelated enolic form as shown, since it shows carbonyl absorption at 1650 cm^{-1} and enol ether double bond absorption at 1620 cm^{-1}. The diastereotopic methylene protons of the ethyl group appear as quartets at δ 4.14 and 4.16 ppm.

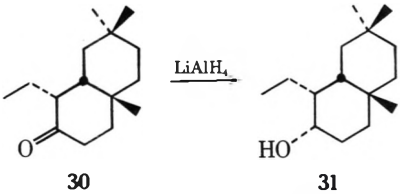
Lithium aluminum hydride reduction of 26[9] affords allylic alcohol 27 in high yield. The ^1H NMR spectrum of alcohol 27



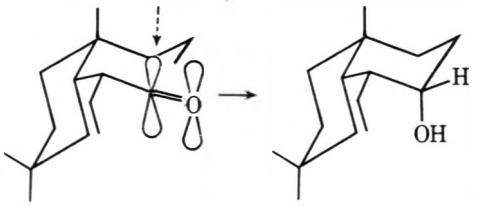
indicates that the hydroxy group occupies the equatorial position. The carbinol proton appears as a broad absorption ($W_{1/2}$ = 15 Hz, δ 4.15 ppm) characteristic of an axial proton.[10] The corresponding proton in acetate 28 appears at δ 5.32 ppm and has $W_{1/2}$ = 15 Hz. Since the *gem*-dimethyl group should fix the decalin in a single chair–chair conformation, it appears that attack of hydride on the presumed intermediate enone 29 occurs exclusively from the axial direction. Such axial at-



tack in a cyclohexanone having an axial substituent at C-3 is unusual. For example, decalone 30 undergoes reduction exclusively to axial alcohol 31, in which the carbinol proton ap-

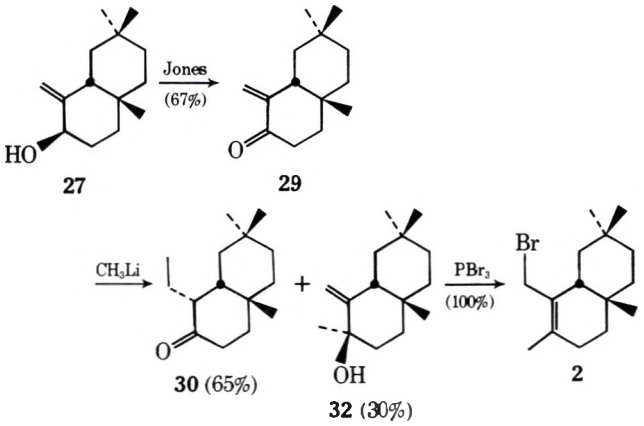


pears as a double doublet (J = 3 and 5 Hz) centered at δ 3.82 ppm. In this case, attack of hydride occurs from the equatorial direction.



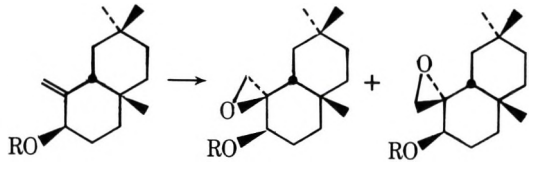
30 31

Oxidation of allylic alcohol **27** (Jones reagent[11]) affords enone **29** in 67% yield. Enone **29** reacts with methyllithium in ether to give the 1,4-addition product **30** in 65% yield, along with 30% of the 1,2-addition product **32**. Ketone **30** and alcohol **32** are conveniently separable by column chromatography. Treatment of tertiary allylic alcohol **32** with phosphorus tribromide in ether gives primary allylic bromide **2** in quantitative yield.



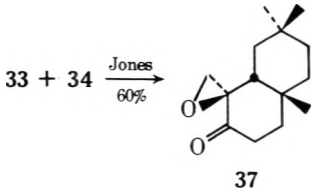
27 29 30 (65%) 32 (30%) 2

Although the synthesis of our target compound **2** was achieved in this manner, the large amount of 1,4 addition to enone **29** precludes the use of this route for viable synthesis. Consequently, we examined other methods for elaboration of alcohol **27**. Oxidation with *m*-chloroperoxybenzoic acid (MCPA) affords epoxy alcohols **33** and **34** in a ratio of 3:1. The predominant top-face oxidation of the double bond appears to be only in part due to direction by the hydroxy group, as acetate **28** gives epoxy acetates **35** and **36** in a ratio of 3:2.



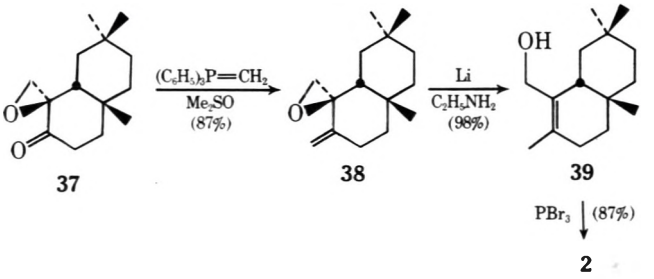
27, R = H **33**, R = H **34**, R = H
28, R = CH_3CO **35**, R = CH_3CO **36**, R = CH_3CO

Jones oxidation[11] of the mixture of **33** and **34** gives keto epoxide **37** in 60% yield after purification. The oxidation



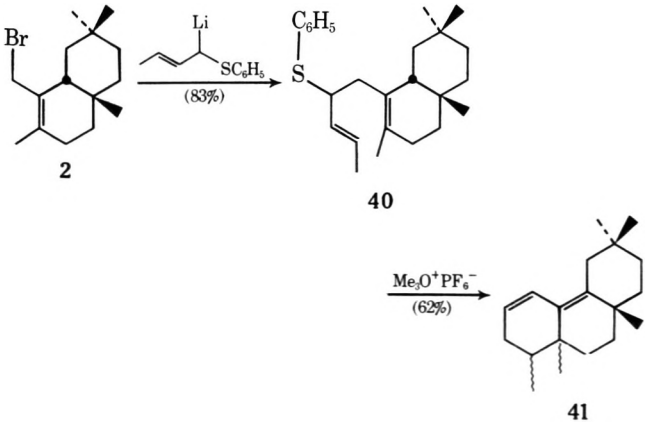
37

product from the minor isomer **34** is presumably lost in purification. Wittig methylenation of **37**, under forcing conditions (see Experimental Section), affords epoxy alkene **38** in yields as high as 87%. Reduction of unsaturated epoxide **38** with lithium in anhydrous ethylamine affords allylic alcohol **39**, which reacts with phosphorus tribromide in ether to give allylic bromide **2** as the sole product. After completion of this work,[1a] van Tamelen, Seiler, and Wierenga reported an alternative synthesis of compound **2**,[12] which they utilized in a biomimetic synthesis of δ-amyrin, β-amyrin, and germanicol. Horan, McCormick, and Arigoni have utilized a sample of **2**, prepared in our laboratory, in an in vivo synthesis of β-amyrin.[13]



37 38 39 2

Preliminary experiments directed toward the further elaboration of allylic bromide **2** have been encouraging. Bromide **2** reacts with phenyl crotyl sulfide anion to give sulfide **40**. When this material is treated with trimethyloxonium hexafluorophosphate in methylene chloride, diene **41** may be



2 40 41

isolated in approximately 60% yield. The structure of **41** is assigned on the basis of its composition and ^1H NMR and uv spectra (one vinyl H, λ_{max} 244 nm, ϵ 4710 M^{-1}). The stereochemistry of this material has not been ascertained. Further experiments will be directed toward coupling bromide **2** with a synthon for rings A and B[2] and completing a synthesis of a pentacyclic triterpene by this route.

Experimental Section

Melting points (Pyrex capillary) are uncorrected. The following instrumentation was used to record spectra: infrared (ir), Perkin-Elmer 137 and 237; ultraviolet (uv), Perkin-Elmer 202; mass spectra, Varian MS-12, Varian M-66, and Consolidated 21-110B; proton magnetic resonance (^1H NMR), Varian A-60 and T-60. The line positions for ^1H NMR spectra are given in the δ scale as parts per million downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in the order (number of protons, multiplicity, proton assignments). Gas–liquid partition chromatography (GLC) analyses were performed on a Varian Aerograph 90-P instrument. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, Calif.

2,5,5-Trimethyl-2-(3-oxobutyl)cyclohexane-1,3-dione (5). A solution containing 105.2 g (0.684 mol) of dione **4**,[4] 1000 ml of methanol, 100 g (1.43 mol) of methyl vinyl ketone, and 1.5 g of potassium hydroxide was refluxed for 27 h. The solvent was evaporated and the residue was diluted with ether, washed with 10% aqueous sodium carbonate and water, and then dried over magnesium sulfate. Evaporation of the solvent yielded 152.5 g (100%) of a yellow oil. Examination of this oil by ^1H NMR showed it to be almost entirely trione **5** with a small amount of dione **6** present: ^1H NMR (CCl_4) δ 0.88 (3 H, s, Me), 1.07 (3 H, s, Me), 1.14 (3 H, s, Me), 2.03 (3 H, s, acetyl Me); ir (neat) 1735, 1700 cm^{-1}.

4a,7,7-Trimethyl-4,4a,7,8-tetrahydronaphthalene-2(3*H*),-5(6*H*)-dione (6). A mixture containing 149.3 g (0.667 mol) of trione **5** and 55 g of *p*-toluenesulfonic acid in 3000 ml of benzene was refluxed with separation of water. After 48 h, the solution was cooled, washed

with 10% aqueous sodium carbonate and water, and then dried over magnesium sulfate. Evaporation of solvent gave 131.1 g of a red-brown solid. Distillation yielded 84.4 g of a yellow solid (bp 125–140 °C at 0.2 Torr) which was washed with hexane to yield 79.3 g (58%) of white dione **6**: mp 92–92.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.78 (3 H, s, Me), 1.16 (3 H, s, Me), 1.43 (3 H, s, Me), 5.79 (1 H, d, vinyl H); ir (CCl_4) 1715, 1675, 1620 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.47; H, 8.61.

2-Ethoxy-4a,7,7-trimethyl-3,4,6,7-tetrahydronaphthalen-5(4a*H*)-one (7). A solution containing 13.5 g (65.5 mmol) of dione **6**, 10.4 g (70.5 mmol) of triethyl orthoformate, 50 ml of benzene, and 1 ml of 95% ethanol containing 2 drops of concentrated hydrochloric acid was refluxed for 3.5 h, then cooled and poured into 5% aqueous sodium hydroxide. After base extraction, the organic phase was washed with water and dried over $MgSO_4$. Evaporation of the solvent yielded 15.1 g of yellow oil which was distilled to give 14.2 g (93%) of light yellow oil (bp 113–114 °C at 0.4 Torr). The ^{1}H NMR spectrum showed that the keto enol ether **7** was the sole product: ^{1}H NMR (CCl_4) δ 0.98 (3 H, s, Me), 1.13 (3 H, s, Me), 1.20 (3 H, s, Me), 1.27 (3 H, t, Me, J = 7 Hz), 3.74 (2 H, q, OCH_2, J = 7 Hz), 5.10 (2 H, broad s, vinyl H).

4a,7,7-Trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (8). A. A solution prepared from 19.0 g (81.3 mmol) of keto enol ether **7**, 500 ml of diethylene glycol, and 130 ml of hydrazine hydrate was warmed to 120 °C over a 2-h period and maintained at this temperature for 30 min. After cooling to 40 °C, 60 g (1.07 mol) of potassium hydroxide was added and the resulting mixture was heated with concurrent distillation until the pot temperature reached 210 °C. After cooling, the reaction mixture and distillate were combined and extracted with petroleum ether. The organic phase was washed with water and dried over magnesium sulfate, and the solvent was evaporated to yield 16.1 g of light yellow liquid: ^{1}H NMR (CCl_4) δ 0.92 (3 H, s, Me), 0.96 (3 H, s, Me), 0.99 (3 H, s, Me), 1.26 (3 H, t, Me, J = 6 Hz), 3.69 (2 H, q, $-OCH_2-$, J = 7 Hz), 4.82 (1 H, s, vinyl H), 4.95 (1 H, d, vinyl H, J = 2 Hz). This material was stirred overnight in 175 ml of *p*-dioxane containing 50 ml of 10% sulfuric acid. After dilution with water, the product was isolated by ether extraction. The organic phase was washed with water and dried over $MgSO_4$, and the solvent was evaporated to yield 8.6 g (55%) of light yellow liquid: ^{1}H NMR (CCl_4) δ 0.74 (3 H, s, Me), 0.94 (3 H, s, Me), 1.11 (3 H, s, Me), 5.43 (1 H, d, vinyl H); ir (neat) 1670, 1610 cm^{-1}. Recrystallization of the 2,4-dinitrophenylhydrazone from methanol gave red plates, mp 149.5–150.5 °C (lit.[3] mp 148.5–150 °C).

Anal. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 61.03; H, 6.66; N, 14.94.

B. A mixture of 20.0 g (0.14 mol) of ketone **11**, 16.0 g (0.23 mol) of methyl vinyl ketone, 0.1 ml of concentrated sulfuric acid, and 40 ml of benzene was refluxed for 130 h. After 10 h, another 0.5 ml of acid was added. The black mixture was diluted with 50 ml of hexane, washed with 5% sodium hydroxide and water, dried ($MgSO_4$), and evaporated. Short-path distillation with an open flame gave a yellowish liquid which was fractionally distilled to give 16.7 g (60.9%) of clear liquid, bp 86–88 °C (0.2 Torr). The material prepared in this manner was identical spectrally with the material prepared as outlined in part A.[14]

2,5,5-Trimethylcyclohex-2-en-1-ol (9). To a stirring mixture of 89.5 g (2.37 mol) of lithium aluminum hydride in 3 l. of ether was added 121.4 g (0.789 mol) of dione **4**[4] over a period of 1 h. Stirring was continued for 88 h and the excess hydride was then decomposed by the addition of aqueous potassium hydroxide. The reaction mixture was filtered and dried over $MgSO_4$, and the solvent was removed in vacuo to yield 94.5 g (85.7%) of colorless liquid: ^{1}H NMR (CCl_4) δ 0.88 (3 H, s, C-5 Me), 0.96 (3 H, s, C-5 Me), 1.69 (3 H, s, C-2 Me), 2.18 (1 H, s, OH), 3.84 (1 H, unresolved double t, C-1 H), 5.22 (1 H, unresolved m, vinyl H); ir (CCl_4) 3350 cm^{-1}.

2,5,5-Trimethylcyclohex-2-en-1-one (10). To a vigorously stirring solution of 93.7 g (0.67 mol) of alcohol **9** in 400 ml of benzene at 5 °C was added a solution prepared from 80.0 g (0.268 mol) of sodium dichromate dihydrate, 335 ml of water, 108 ml of concentrated sulfuric acid, and 35 ml of glacial acetic acid over a 2.5-h period. After an additional 3 h of stirring, the phases were separated and the aqueous portion extracted once with benzene. The combined organic phases were washed with 10% aqueous sodium carbonate and water, then dried over $MgSO_4$. The solvent was distilled at atmospheric pressure to yield 84.0 g (90.8%) of faintly yellow liquid residue. The ^{1}H NMR spectrum of this crude product revealed less than 5% of the β,γ-unsaturated isomer as the only impurity.

2,5,5-Trimethylcyclohexanone (11). A mixture containing 83.4 g (0.61 mol) of enone **10**, 135 ml of ethyl acetate, and 1.0 g of 10% palladium on carbon was hydrogenated (Parr apparatus). After 18 h, the mixture was filtered and the solvent was removed by distillation at atmospheric pressure to obtain 81.1 g (95.7%) of light yellow liquid residue. This was distilled to yield 70.9 g (83.8%) of colorless liquid: bp 75–80 °C (18–22 Torr); ^{1}H NMR (CCl_4) δ 0.80 (3 H, s, C-5 Me), 0.92 (3 H, d, C-2 Me, J = 6 Hz), 1.04 (3 H, s, C-5 Me); ir (CCl_4) 1710 cm^{-1}. The 2,4-dinitrophenylhydrazone was obtained as yellow-orange needles after recrystallization from methanol, mp 121–122 °C (lit.[3] mp 117–119 °C).

Anal. Calcd for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29; N, 17.49. Found: C, 56.05; H, 6.37; N, 17.35.

4aβ,7,7-Trimethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (12). To 18.5 g (96.4 mmol) of enone **8** in 200 ml of ethyl acetate was added 1.4 g of platinum oxide. This was hydrogenated until hydrogen uptake ceased (6 min), then the mixture was filtered and the solvent evaporated to yield 18.4 g (99%) of ketone **12**. Crystallization from hexane gave white plates: mp 68–69 °C; ^{1}H NMR ($CDCl_3$) δ 0.92 (6 H, s, Me), 1.25 (3 H, s, Me); ir (CCl_4) 1720 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.28; H, 11.44.

4aβ,7,7-Trimethyl-10aβ-decahydronaphthalene (14). This hydrocarbon was prepared by Wolff–Kishner reduction of ketone **11** and dione **16**[6] by the following general procedure. A solution containing 0.9 mmol of ketone **11** or dione **16**, 8 ml of freshly distilled diethylene glycol, and 2 ml of 85% hydrazine hydrate was heated at 120 °C for 3 h and then cooled to room temperature. The flask was fitted for distillation, 1 g of KOH was added, and the alkaline mixture was heated to 210 °C over a 5-h period, then maintained at this temperature for an additional 1 h. The combined distillate and reaction mixture was partitioned between ether and water. The phases were separated and the ether phase was washed well with water. After drying over $MgSO_4$, the ether was evaporated to obtain the hydrocarbon product. Analysis by GLC (100 ft × 0.01 in. Apeizon L, 115 °C, He flow 2.5 ml/min) showed that the hydrocarbons obtained from ketone **11** and dione **16** are identical, and different from the hydrocarbon (**15**) obtained from a similar Wolff–Kishner reduction of *trans*-decalone **13**.

3α-Bromo-4aβ,7,7-trimethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (17). To 5.83 g (30.0 mmol) of ketone **12** in 50 ml of glacial acetic acid was added 4.79 g (30.0 mmol) of bromine in 40 ml of glacial acetic acid. The bromine color was discharged immediately upon addition, and the resulting yellow-brown solution was stirred for 19 h, diluted with water, and extracted with benzene. The organic phase was thoroughly washed with water and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 8.36 g (100%) of light yellow bromo ketone **17**: ^{1}H NMR ($CDCl_3$) δ 0.95 (6 H, s, two Me), 1.39 (3 H, s, Me), 4.96 (1 H, dd, C-3 H, J = 14 and 7 Hz); ir (neat) 1735 cm^{-1}.

Anal. Calcd for $C_{13}H_{21}OBr$: C, 57.25; H, 7.69; Br, 29.24. Found: C, 57.09; H, 7.85; Br, 29.22.

4aβ,7,7-Trimethyl-4a,5,6,7,8,8aβ-hexahydronaphthalen-2(1*H*)-one (18). A mixture containing 8.36 g (30.0 mmol) of crude bromo ketone **17**, 12.7 g (127 mmol) of calcium carbonate, and 100 ml of dimethylacetamide was warmed to 180 °C over a 1-h period and maintained at this temperature for an additional 20 min. After cooling the calcium carbonate was decomposed by the addition of 10% HCl. The crude product was extracted with benzene, washed with water, and dried ($MgSO_4$). Evaporation of the solvent gave 5.68 g of brown liquid which was distilled to yield 5.05 g of yellow liquid, bp 74–92 °C (0.2–0.3 Torr). The ^{1}H NMR spectrum of this material revealed the presence of a small amount (10–20%) of enone **8**, in addition to enone **18**. These were separated by chromatography on neutral alumina by elution with pentane/ether. A trace amount of dienone **19** was also isolated.

Enone 18: ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, s, Me), 0.90 (3 H, s, Me), 1.22 (3 H, s, Me), 2.00 (1 H, d, C-1 equatorial H, J = 17 Hz), 2.83 (1 H, dd, C-1 axial H, J = 17 and 5 Hz), 5.83 (1 H, d, C-3 vinyl H, J = 10 Hz), 6.47 (1 H, dd, C-4 vinyl H, J = 10 and 2 Hz); ir (neat) 1680, 1635 cm^{-1}. The 2,4-dinitrophenylhydrazone was prepared and recrystallized from methanol. The material was obtained as red plates, mp 143.5–144.0 °C.

Anal. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 61.22; H, 6.63; N, 15.08.

Dienone 19: ^{1}H NMR (CCl_4) δ 0.72 (3 H, s, Me), 1.02 (3 H, s, Me), 1.18 (3 H, s, Me), 5.82 (1 H, unresolved m, C-1 vinyl H), 5.90 (1 H, dd, C-3 vinyl H, J = 10 and 2 Hz), 6.64 (1 H, d, C-4 vinyl H, J = 10 Hz); ir (neat) 1660, 1630 cm^{-1}. The 2,4-dinitrophenylhydrazone was prepared and recrystallized from methanol as red plates, mp 147–149 °C.

Anal. Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C,

61.83; H, 5.75; N, 15.09.

1-Carboxy-4a,7,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (22). Sodium hydride (0.25 g of a 55.2% mineral oil dispersion, 5.8 mmol) was added to an oven-dried three-neck flask fitted with a reflux condenser, a magnetic stirrer, and a rubber septum. After washing the solid twice with anhydrous hexane, a solution of 22 ml of dimethyl sulfoxide and 1.0 g (5.2 mmol) of enone 8 was added. The mixture was stirred until hydrogen evolution had ceased (2 h) and the dimethyl sulfoxide was removed by distillation in vacuo. The dark residue was dissolved in 20 ml of anhydrous ether and poured into a stirring slurry of 50 ml of ether and crushed dry ice (prepared in a glove bag) cooled in a dry ice/isopropyl alcohol bath. After 6 h, the bath was removed and stirring was continued overnight. The product was extracted with 0.02 N sodium hydroxide. After washing the basic solutions with ether, they were cooled, acidified, and extracted with methylene chloride. The organic solutions were washed with water, dried ($MgSO_4$), and evaporated to afford 770 mg (61.1%) of semisolid material: ^1H NMR ($CDCl_3$) δ 0.90 (3 H, s, Me), 1.10 (3 H, s, Me), 1.32 (3 H, s, Me), 11.18 (1 H, broad s, COOH).

Anal. Calcd for $C_{14}H_{20}O_3$: mol wt, 215.9847. Found: 215.9839 (high-resolution mass spectrum).

The neutral fractions from the extraction were shown by ^1H NMR to be a mixture of enone **8** and its β,γ isomer.

Attempted recrystallization of the acid or its sodium salt was unsuccessful. Some decarboxylation occurred during these attempts at purification. If the final product was isolated by filtration rather than extraction, the monohydrate was isolated as a fine, white solid, mp 100 °C dec.

Anal. Calcd for $C_{14}H_{20}O_3 \cdot H_2O$: C, 66.12; H, 8.72. Found: C, 66.41; H, 8.58.

1-(Methoxycarbonyl)-4a,7,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (23). Excess diazomethane was added to a solution of 190 mg (0.8 mmol) of **22** and 1 ml of ether, followed by dropwise addition of acetic acid to decompose the excess methylating agent. The resulting solution was evaporated to give 200 mg (100%) of liquid which solidified upon standing. Recrystallization from hexane gave the analytical sample: mp 71.5–72.5 °C; ir (CCl_4) 1742, 1684, 1629, 1462, 1429, 1348, 1326, 1318, 1290, 1236, 1024, 866 cm^{-1}; ^1H NMR (CCl_4) δ 0.83 (3 H, s, Me), 1.00 (3 H, s, Me), 1.25 (3 H, s, Me), 3.68 (3 H, s, Me).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.61; H, 8.68.

1-(Ethoxycarbonyl)-4a,7,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (25). This material was prepared by the procedure reported in ref 1b, p 76: ^1H NMR (CCl_4) δ 0.80 (3 H, s, Me), 1.0 (3 H, s, Me), 1.23 (3 H, s, Me), 1.24 (3 H, t, ester Me, J = 7 Hz); ir (CCl_4) 1735, 1680, 1620 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.73; H, 8.96.

1-(Ethoxycarbonyl)-4aβ,7,7-trimethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphth-2-ol (26). A mixture of 14.53 g (55 mmol) of β-keto ester **25**, 1.5 g of 10% palladium on carbon, and 150 ml of ethyl acetate was hydrogenated on a Parr apparatus for 16 h. The reaction mixture was filtered and the solvent removed in vacuo to yield 14.56 g (100%) of enolic β-keto ester **26** which solidified on standing. Recrystallization from hexane gave the analytical sample: mp 35.0–38.0 °C; ^1H NMR (CCl_4) δ 0.88 (3 H, s, Me), 0.94 (6 H, s, two Me), 1.28 (3 H, t, ester Me, J = 7 Hz), 4.14 (1 H, q, $-OCH_2CH_3$, J = 7 Hz), 4.16 (1 H, q, $-OCH_2CH_3$, J = 7 Hz); ir (CCl_4) 1650, 1620 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.22; H, 9.57.

4aβ,7,7-Trimethyl-1-methylene-8aβ-decahydronaphth-2β-ol (27). To a stirring mixture of 13.87 g (366 mmol) of lithium aluminum hydride in 500 ml of ether was added 24.39 g (91.7 mmol) of β-keto ester **26** in 150 ml of ether over a period of 1 h. Stirring was continued for 22 h and the excess hydride was then decomposed by the successive addition of 14 ml of water, 14 ml of 15% aqueous potassium hydroxide, and 42 ml of water. The mixture was filtered and dried and the solvent was removed in vacuo to give 17.1 g (97.5%) of colorless liquid which crystallized upon standing overnight. The analytical sample (mp 82–83 °C) was prepared by recrystallization from hexane: ^1H NMR (CCl_4) δ 0.92 (9 H, s, three Me), 3.14 (1 H, broad s, CHOH), 4.15 (1 H, broad unresolved m, CHOH), 4.68 (1 H, broad t, vinyl H), 4.92 (1 H, broad t, vinyl H); ir (CCl_4) 3650, 3320, 1655, 905 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.57; H, 11.46.

Alcohol **27** was acetylated for 18 h at room temperature with acetic anhydride in pyridine. Acetate **28** was obtained in about 90% yield: ^1H NMR (CCl_4) δ 0.93 (3 H, s, Me), 0.95 (6 H, s, Me's), 2.00 (3 H, s, CH_3CO), 4.75 (2 H, m, vinyl H's), 5.32 (1 H, broad m, $W_{1/2}$ = 22 Hz, >CHOAc); ir (neat) 1740, 1650 cm^{-1}.

4aβ,7,7-Trimethyl-1-methylene-1,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(3*H*)-one (29). To a solution of 1.85 g (8.87 mmol) of alcohol **27** in 60 ml of acetone, cooled in an ice bath, was added 8 ml (32 mmol) of Jones reagent.[11] After 15 min, the excess oxidant was decomposed by the addition of 4 ml of isopropyl alcohol. The reaction mixture was diluted with ether and water and the organic phase was washed with 10% aqueous sodium carbonate and water, then dried. The solvent was removed to yield 1.23 g (67.4%) of slightly yellow liquid: ^1H NMR (CCl_4) δ 0.84 (3 H, s, Me), 0.88 (3 H, s, Me), 1.00 (3 H, s, Me), 4.90 (1 H, d, vinyl H, J = 2 Hz), 5.56 (1 H, d, vinyl H, J = 2 Hz); ir (CCl_4) 1685, 1615 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O$: mol wt, 206.1671. Found: 206.1677 (high-resolution mass spectrum).

1α-Ethyl-4aβ,7,7-trimethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (30) and 2α,4aβ,7,7-Tetramethyl-1-methylene-8aβ-decahydronaphth-2β-ol (32). To a stirring solution of 10.95 ml (17.5 mmol) of 1.64 M methyllithium in ether was added 1.203 g (5.84 mmol) of enone **29** in 20 ml of ether over a 10-min period. After an additional 1 h of stirring, the excess methyllithium was decomposed by the addition of 1 ml of 10% HCl. The reaction mixture was diluted with 10% HCl and ether and the layers separated. The organic phase was washed with water and dried. The solvent was removed to yield 1.204 g of light yellow liquid. Spectral analysis of the crude product showed it to be a mixture of starting material, alcohol **32**, and ketone **30**, in a ratio of 1:3:7 (based on ^1H NMR). The two products were isolated by chromatography on 50 g of basic alumina (activity 1) eluting with hexane/ether, and purified by crystallization from hexane.

Ketone 30: mp 59–61 °C; ^1H NMR (CCl_4) δ 0.83 (3 H, s, Me), 0.90 (3 H, s, Me), 1.28 (3 H, s, Me); ir (CCl_4) 1710 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.75; H, 11.78.

Alcohol 32: mp 82–83.5 °C; ^1H NMR (CCl_4) δ 0.94 (9 H, s, three Me), 1.34 (3 H, s, Me), 4.72 (1 H, d, vinyl H, J = 2 Hz), 5.18 (1 H, d, vinyl H, J = 2 Hz); ir (CCl_4) 3650, 3525, 1630, 915 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.19; H, 11.63.

1α-Ethyl-4aβ,7,7-trimethyl-8aβ-decahydronaphth-2α-ol (31). To 26.5 mg (0.7 mmol) of lithium aluminum hydride in 0.8 ml of ether was added 39.0 mg (0.175 mmol) of ketone **30** in 1.4 ml of ether. After stirring for 20 h, the excess hydride was decomposed by the successive addition of 25 ml of water, 25 ml of 15% aqueous KOH, and 75 ml of water. The reaction mixture was diluted with ether and the layers separated. The ether layer was dried ($MgSO_4$) and the solvent removed in vacuo to give 35.0 mg of colorless liquid: ^1H NMR (CCl_4) δ 0.82 (3 H, s, Me), 0.92 (3 H, s, Me), 0.96 (3 H, s, Me), 3.81 (1 H, q, CHOH, J = 5 Hz); ir (CCl_4) 3650, 3320, 1460, 1040, 1005, 952, 932 cm^{-1}.

Anal. Calcd for $C_{15}H_{28}O$: mol wt, 224.2140. Found: 224.2141 (high-resolution mass spectrum).

1,4aβ,7,7-Tetramethyl-1β,9-oxido-8aβ-decahydronaphth-2β-ol (33) and 4aβ,7,7-Trimethyl-1α,9-oxido-8aβ-decahydronaphth-2β-ol (34). To a stirring solution of 10.0 g (48.1 mmol) of allylic alcohol **27** in 150 ml of chloroform, cooled in an ice bath, was added 10.76 g (53 mmol) of 85% *m*-chloroperoxybenzoic acid in a mixture of 90 ml of chloroform and 10 ml of 95% ethanol. The oxidant was added dropwise over a period of 45 min. The reaction mixture was stirred for 16 h, during which time it warmed to room temperature. Excess peroxy acid was decomposed by the addition of 20% aqueous sodium sulfite. The organic phase was washed with 10% aqueous NaOH and water and then dried. The solvent was removed to give 10.90 g (100%) colorless liquid which crystallized upon standing. The crude product contained **33** and **34** in a ratio, as judged by its ^1H NMR spectrum, of 3:1. Two crystallizations from hexane gave epoxy alcohol **33** as a white solid: mp 90.5–92.0 °C; ^1H NMR (CCl_4) δ 0.84 (3 H, s, Me), 0.94 (3 H, s, Me), 0.98 (3 H, s, Me), 2.36 (1 H, d, epoxy CH, J = 6 Hz), 2.60 (1 H, d, CHOH, J = 3 Hz), 3.08 (1 H, d, epoxy CH, J = 6 Hz), 3.88 (1 H, broad m, CHOH); ir (CCl_4) 3630, 3520, 938, 896 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.20; H, 10.51.

1,4aβ,7,7-Tetramethyl-1β,9-oxido-3,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(1*H*)-one (37). To a stirring solution of 10.8 g (48.7 mmol) of a 3:1 mixture of epoxy alcohols **33** and **34** in 250 ml of acetone, cooled in an ice bath, was added 40 ml (160 mequiv) of Jones reagent[11] over 1 min. Stirring was continued at 0 °C for 15 min, and the excess Jones reagent was then decomposed by the addition of 20 ml of isopropyl alcohol. The reaction mixture was diluted with ether and water and the organic phase was washed with 10% aqueous Na_2CO_3 and water, then dried. The solvent was removed to give 6.22

g of a slightly yellow solid. Crystallization from hexane gave the analytical sample: mp 93–93.7 °C; ^{1}H NMR (CCl_4) δ 0.86 (3 H, s, Me), 0.95 (3 H, s, Me), 1.28 (3 H, s, Me), 2.79 (2 H, s, epoxy CH_2); ir (CCl_4) 1720, 890 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.46; H, 9.99.

1,4aβ,7,7-Tetramethyl-2-methylene-1β,9-oxido-8aβ-decahydronaphthalene (38). A 488-mg sample of 56.8% sodium hydride in mineral oil (11.54 mmol of sodium hydride) was washed several times with hexane under a nitrogen atmosphere. The last traces of hexane were removed under a nitrogen stream and 12.5 ml of dimethyl sulfoxide was added. The mixture was heated at 75 °C under nitrogen until evolution of hydrogen ceased (50 min). The solution was cooled to room temperature and 4.09 g (11.54 mmol) of methyltriphenylphosphonium bromide was added. Solution was effected by mild warming, and the clear yellow liquid was then allowed to stand at room temperature for 30 min. A 1.28-g (5.77 mmol) portion of epoxy ketone **37** was added to the ylide solution and the resulting mixture was heated at 75 °C until no starting material could be observed by TLC analysis (21 h). The reaction mixture was partitioned between hexane and water. After separation, the organic phase was washed with water and dried. The solvent was removed to obtain a light yellow liquid containing a small amount of orange solid. The crude product was taken up in hexane and the triphenylphosphine oxide precipitated after refrigeration at −30 °C for 24 h. Filtration and solvent removal gave 1.10 g (87%) of epoxide **38** as a slightly yellow liquid: ^{1}H NMR (CCl_4) δ 0.83 (3 H, s, Me), 0.93 (3 H, s, Me), 1.10 (3 H, s, Me), 2.40 (1 H, d, epoxy CH, J = 7 Hz), 2.58 (1 H, d, epoxy CH, J = 7 Hz), 4.63 (1 H, unresolved m, vinyl H), 4.80 (1 H, unresolved m, vinyl H); ir (CCl_4) 1655, 1470, 965, 925, 913, 900 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O$: mol wt, 220.1827. Found: 220.1833 (high-resolution mass spectrum).

Yields in this reaction average 70%. It is critical that this reaction be performed under strictly anhydrous conditions.

1-Hydroxymethyl-2,4aβ,7,7-tetramethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalene (39). To a solution of 624 mg (2.84 mmol) of allylic epoxide 38 in 100 ml of ethylamine (distilled from sodium) was added 43.0 mg (6.2 mmol) of lithium. The reaction mixture was stirred for 1.5 h at reflux. Excess lithium was decomposed by the addition of sodium nitrite and the solvent removed under a nitrogen stream. The residue was partitioned between saturated ammonium chloride and ether. The layers were separated and the organic phase was washed with water, dried ($MgSO_4$), and evaporated in vacuo to obtain 619 mg (98%) of light yellow liquid: ^{1}H NMR (CCl_4) δ 0.82 (3 H, s, Me), 0.88 (3 H, s, Me), 0.92 (3 H, s, Me), 1.61 (3 H, s, vinyl Me), 2.40 (1 H, s, OH), 3.77 (1 H, d, CHOH, J = 11 Hz), 4.06 (1 H, d, CHOH, J = 11 Hz); ir (CCl_4) 3650, 3450 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}O$: mol wt, 222.1983. Found: 222.1986 (high-resolution mass spectrum).

1-Bromomethyl-2,4aβ,7,7-tetramethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalene (2). A. To 50 mg (0.23 mmol) of tertiary allylic alcohol **32** in 1.5 ml of ether was added 0.034 ml (0.36 mmol) of phosphorus tribromide. After stirring for 16 h, the reaction mixture was diluted with ether, washed with 5% aqueous Na_2CO_3 and water, and dried ($MgSO_4$). Removal of the solvent in vacuo afforded 60 mg (93.5%) of bromide **2** as a light yellow liquid: ^{1}H NMR (CCl_4) δ 0.86 (3 H, s, Me), 0.94 (3 H, s, Me), 0.97 (3 H, s, Me), 1.68 (3 H, s, vinyl Me), 3.66 (1 H, d, CHBr, J = 10 Hz), 4.13 (1 H, d, CHBr, J = 10 Hz); ir (CCl_4) 2940, 1020 cm^{-1}.

Anal. Calcd for $C_{15}H_{25}Br$: mol wt, 284.1141. Found: 284.1131 (high-resolution mass spectrum).

B. To 400 mg (1.80 mmol) of primary allylic alcohol **39** in 25 ml of ether was added 0.35 ml (3.68 mmol) of phosphorus tribromide. The reaction mixture was stirred for 22 h and then washed with 5% aqueous Na_2CO_3 and water. After drying ($MgSO_4$), the solvent was removed to give 447 mg (87%) of bromide **2** as a faintly yellow liquid. Spectra (^{1}H NMR and ir) of this compound were identical with those obtained for the product prepared by method A.

1-(2-Thiophenyl-3-pentenyl)-2,4aβ,7,7-tetramethyl-3,4,4a,-5,6,7,8,8aβ-octahydronaphthalene (40). A magnetically stirred solution of 540 mg (3.29 mmol) of crotyl phenyl sulfide, 5.66 ml of diazabicyclooctane solution (0.56 M in tetrahydrofuran, 3.16 mmol), and 4.5 ml of anhydrous THF under nitrogen was cooled to −20 °C (carbon tetrachloride/dry ice). n-Butyllithium (1.49 ml, 2.17 M in hexane, 3.24 mmol) was added and the resulting yellow-orange solution stirred for 30 min. A mixture of 450 mg (1.58 mmol) of bromide **2** and 2.7 ml of THF was added and stirring was continued for another 30 min. After 15 min, a solid (probably lithium bromide) began to separate. The bath was removed and after another 1 h, the reaction was quenched with ammonium chloride. The product was diluted with ether, washed with water, saturated brine, dried ($MgSO_4$), and evaporated to give 570 mg of yellowish oil. After Kugelrohr distillation (60 °C, 0.5 Torr) to remove the excess crotyl sulfide, the product was chromatographed (10 g of silica gel, hexane) to give 480 mg (82.6%) of clear oil: ^{1}H NMR (CCl_4) δ 0.83 (3 H, s, Me), 0.90 (6 H, s, Me's), 1.55 (3 H, broad s, Me), 3.46 (1 H, m, >$CHSC_6H_5$), 5.20 (2 H, m, vinyl H's), 7.16 (5 H, m, aromatic H's); ir (neat) 1479, 1458, 1437, 1376, 1361, 963, 739, 691 cm^{-1}.

Anal. Calcd for $C_{25}H_{36}S$: mol wt, 368.2540. Found: 368.2583 (high-resolution mass spectrum).

1,6,6,8a,10a-Pentamethyl-1,2,5,6,7,8,8a,9,10,10a-decahydrophenanthrene (41). A solution of 210 mg (0.56 mmol) of **40**, 220 mg (1.08 mmol) of trimethyloxonium hexafluorophosphate, and 10 ml of methylene chloride was stirred under nitrogen for 4 h. After quenching with saturated Na_2CO_3, the deep purple solution slowly changed to red and then to yellow-orange. The solvent was removed in vacuo and the residue was taken up in ether, washed with water and saturated brine, dried ($MgSO_4$), and evaporated to afford 170 mg of yellow-orange oil. Preparative TLC (hexane) gave 89 mg (61.5%) of yellow oil: ^{1}H NMR (CCl_4) δ 0.88 (18 H, broad s), 5.28 (2 H, broad s, vinyl H's); ir (CCl_4) 1458, 1437 (shoulder), 1377, 1361, 1244, 967, 865 cm^{-1}; uv (hexane) 244 nm (ε 4710).

Anal. Calcd for $C_{19}H_{30}$: mol wt, 258.2348. Found: 258.2344 (high-resolution mass spectrum).

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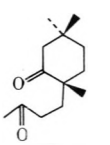
Registry No.—**2**, 59270-12-1; **4**, 1125-11-7; **5**, 59270-13-2; **6**, 24810-40-0; **7**, 59270-14-3; **8**, 17323-26-1; **8** 2,4-DNP, 59270-15-4; **9**, 59270-16-5; **10**, 42747-41-1; **11**, 32543-18-9; **11** 2,4-DNP, 47300-89-0; **12**, 7056-56-6; **17**, 59270-17-6; **18**, 59270-18-7; **18** 2,4-DNP, 59270-19-8; **19**, 59270-20-1; **19** 2,4-DNP, 59270-21-2; **22**, 59270-22-3; **23**, 59270-23-4; **25**, 35482-84-9; **26**, 59270-24-5; **27**, 35482-86-1; **28**, 59270-25-6; **29**, 59270-26-7; **30**, 59270-27-8; **31**, 59270-28-9; **32**, 59270-29-0; **33**, 35482-87-2; **34**, 59331-27-0; **37**, 35482-88-3; **38**, 35482-89-4; **39**, 35482-90-7; **40**, 59270-30-3; **41**, 59270-31-4; methyl vinyl ketone, 78-94-4; bromine, 7726-95-6; diazomethane, 334-88-3; acetic anhydride, 108-24-7; phosphorus tribromide, 7789-60-8; crotyl phenyl sulfide, 702-04-5.

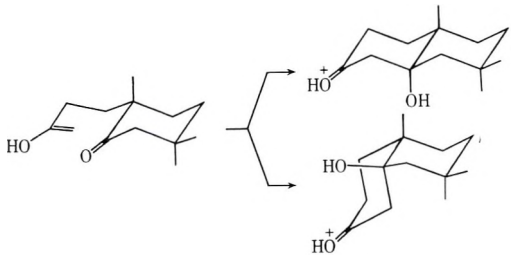
References and Notes

(1) Preliminary communication of portions of this work has appeared previously: (a) C. H. Heathcock and J. E. Ellis, *Chem. Commun.*, 1474 (1971); (b) J. E. Ellis, J. S. Dutcher, and C. H. Heathcock, *Synth. Commun.*, **4**, 71 (1974).
(2) J. S. Dutcher, J. G. Macmillan, and C. H. Heathcock, *J. Org. Chem.*, preceding paper in this issue.
(3) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2431 (1956).
(4) R. D. Clark, J. E. Ellis, and C. H. Heathcock, *Synth. Commun.*, **3**, 347 (1973).
(5) C. H. Heathcock, J. E. Ellis, J. E. McMurry, and A. Coppolino, *Tetrahedron Lett.*, 4995 (1971).
(6) C. H. Heathcock and D. Gray, *Tetrahedron*, **27**, 1239 (1971).
(7) For a discussion of this reaction and optimization of reaction conditions, see ref 1b.
(8) Several attempts to accomplish acid-catalyzed esterification of keto acid **22** were not promising.
(9) (a) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **75**, 939 (1953); (b) E. Roman, A. J. Frey, P. A. Stadler, and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1900 (1957).
(10) (a) A. Hassner and C. H. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964); (b) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 77.
(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(12) E. E. van Tamelen, M. P. Seller, and W. Wierenga, *J. Am. Chem. Soc.*, **94**, 8229 (1972).
(13) H. Horan, J. P. McCormick, and D. Arigoni, *Chem. Commun.*, 73 (1973).
(14) The two stages in this acid-catalyzed Robinson annelation[5] occur with dramatically different rates. The Michael addition, leading to dione i, occurs



i

fairly rapidly; a benzene solution 3.2 M in ketone **11**, 4 M in methyl vinyl ketone, and containing 2.5 ml of concentrated H_2SO_4 per liter of benzene is completely converted into dione i after 16 h reflux. The subsequent aldol condensation of i, leading to enone **8**, requires refluxing a benzene solution



0.55 M in dione i and containing 8 ml of concentrated H_2SO_4 per liter of benzene for 70 h.

The extreme slowness of this aldol condensation is probably due to the fact that a 1,3-diaxial relationship is created in either of the two modes of cyclization shown.

We,[15] and others,[16] have recently found that the acid-catalyzed method of accomplishing Robinson annelations is facilitated in such cases by refluxing the initially formed dione with ethanolic KOH to accomplish the aldol stage of the annelation.

(15) R. D. Clark, E. G. DelMar, and C. H. Heathcock, unpublished observations.

(16) P. M. Worster, Ph.D. Thesis, University of British Columbia, 1975.

Charge Localization in the Carbonium Ions of Methylbenzanthracenes

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Covalent binding of aromatic hydrocarbons to cellular macromolecules, the first probable step in the tumor-initiating process, requires metabolic activation by monooxygenase enzyme systems. Acid-catalyzed proton–deuterium exchange was used as a model to simulate the electrophilic oxygen atom activated by such enzymes. Kinetics of exchange with deuterium ion for a series of carcinogenic and noncarcinogenic methylbenzanthracenes were studied by NMR in two sets of conditions, i.e., CCl_4–CF_3COOD (85:15 v/v and 50:50 v/v). Deuteration of the potent carcinogen 7,12-dimethylbenz[*a*]anthracene at the most basic position C-12 generated a carbonium ion with charge localized at the complementary 7 position, resulting in the specific deuteration of the attached methyl group. Similarly, selective attack of deuterium ion on C-6 in 3-methylcholanthrene produced a carbonium ion with a high degree of charge localization at C-12b and, consequently, specific deuteration at the adjacent methylene group. This study has revealed that charge localization in the carbonium ion renders this intermediate chemically reactive; such a distinctive property might play a role in the bioactivation of these compounds.

The common feature unifying the wide variety of structures of chemical carcinogens is the electrophilic character[1,2] of the reactive species responsible for binding to cellular macromolecules. Reaction of these electrophiles with biological nucleophilic targets constitutes the first essential step that is critical in the succession of events leading to neoplasia. In the case of the inert polycyclic aromatic hydrocarbons, binding activation is supplied by monooxygenase enzymes.[3,4]

From a chemical standpoint the hydroxylation reaction catalyzed by these nonspecific enzyme systems points to an oxygen atom transfer reaction, the reactive species being an oxygen atom with six electrons in its outer shell.[5,6]

Although an enzymic mechanism may be different from any known chemical mechanism, it still must fall within the framework of basic chemical laws, and the use of a chemical model might provide fruitful information on the complex mechanism of metabolic activation of these compounds. Following this line of reasoning, without pretense of simulating the "oxenoid" character of the enzymically activated oxygen but solely its electron-deficient properties, the kinetics of acid-catalyzed proton–deuterium exchange by NMR were studied for a series of carcinogenic and noncarcinogenic methylbenzanthracenes. These experiments compared the relative reactivities of the most basic positions and the relative basicities of different sites in the same molecule.

The purpose of this approach was to evaluate whether it was possible to generalize the proposed mechanism of hydrocarbon activation[7] to an extensive series of carcinogenic hydrocarbons. In such a mechanism, attack of the enzymically catalyzed oxygen atom at the most reactive substituting positions would form electrophilic centers at sites complementary to the points of activation, and such centers may react with cellular targets.

Results and Discussion

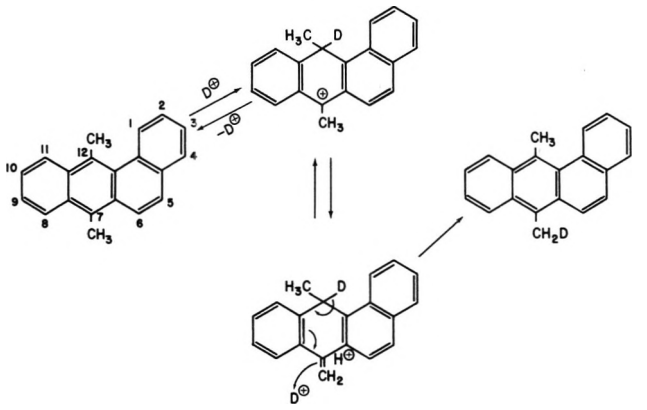
Charge Localization in the Carbonium Ion of 7,12-Dimethylbenz[*a*]anthracene and 3-Methylcholanthrene by NMR. The protonation of 7,12-dimethylbenz[*a*]anthracene (7,12-DMBA) on C-12 in acid medium was previously proposed[8] and charge localization on C-7 in the corresponding arenonium ion was suggested by MO calculations. We have determined the structure of the arenonium ion by comparing the NMR spectra of 7,12-DMBA in neutral and protonated or deuterated acidic solvents (see paragraph at end of paper regarding supplementary material). The ratio of the integrated intensities of the proton peaks in the spectrum of 7,12-DMBA in CCl_4 is, from high to low field, 3:3:5:1:1:2:1. Assignment of the 7-CH_3 (δ 3.00) and 12-CH_3 (δ 3.29) resonances was made by comparison with the spectra of 7-methylbenz[*a*]anthracene (7-MBA) (7-CH_3, δ 3.00) and 12-methylbenz[*a*]anthracene (12-MBA) (12-CH_3, δ 3.32) under the same conditions. A good general correlation exists between the methyl chemical shifts of the 12 monosubstituted methylbenzanthracenes[9] and the corresponding aryl protons of benzanthracene.[10]

The spectrum of 7,12-DMBA in CCl_4–CF_3COOH–H_2SO_4 (volume ratios 50:46.67:3.33) appears generally shifted to lower field with respect to the spectrum in CCl_4. This is attributable to the presence of the positive charge, as well as to the increased polarity of the solvent system. However, the 12-CH_3 group (details of assignment given below) is shifted toward the aliphatic region (δ 1.72) and occurs as a doublet (J = 7.6 Hz). A new quartet at δ 5.61 corresponding to the proton added at the basic 12 position (see below) shows the same coupling constant (J = 7.6 Hz) as the 12-CH_3 doublet. The original compound could be recovered unchanged by dilution with cold water and extraction into CCl_4.

When 7,12-DMBA was dissolved in a mixture of CCl_4–CF_3COOD–D_2SO_4 (volume ratios 50:46.67:3.33), the spectrum showed that the quartet was absent, the 12-CH_3 (δ 1.72) appeared as a singlet, and the 7-CH_3 was entirely exchanged with deuterium when the spectrum was recorded 1 h after dissolution. The solution of 7,12-DMBA in deuterated acid was quenched in D_2O after 1.75 h, and extracted with CCl_4, in which solvent the spectrum was recorded. A comparison of this spectrum with the original 7,12-DMBA spectrum in CCl_4 (see above) demonstrates unequivocally that the 7-CH_3 has been exchanged and the upfield shifted CH_3 group in protonated and deuterated acidic solvents (see above) must necessarily be the one substituted in 12 position.

The mechanism of deuteration of 7,12-DMBA at 7-CH_3 is shown in Scheme I. The selective attack of deuterium ion on

Scheme I



C-12 produces a carbonium ion with a high degree of charge localization at C-7 resulting in an appreciable acidity of the attached methyl group. As a consequence of this effect, the exchange of the proton in the 7-CH_3 is observed. Further stabilization leaves the 7-CH_3 selectively deuterated.

In the case of 3-methylcholanthrene (3-MC), the spectrum was recorded in $CDCl_3$ (see paragraph at end of paper regarding supplementary material) and the assignment of the aliphatic protons was made following the rules described above. The aromatic protons were assigned by comparing the 3-MC spectrum with that of benzanthracene[10] and by applying Martin's empirical rules,[11] which suggest spectral regions for each type of aromatic proton.

The meso-anthracene proton H6 is a singlet[12] and, with the angular proton H7, exhibits the largest downfield shift. The spectrum in $CDCl_3$–CF_3COOH–H_2SO_4 (volume ratios 50:46.67:3.33) shows a two-proton singlet in the aliphatic region (δ 4.75) corresponding to the selective protonation of the meso-anthracenic 6-carbon atom.

The 3-MC spectrum in $CDCl_3$–CF_3COOH–D_2SO_4 (volume ratios 50:46.67:3.33) recorded 0.5 h after preparation of the solution displayed complete exchange of H6 and partial deuteration of 12b-CH_2. The acidic deuterated solution was poured into D_2O after 2 h and extracted with $CDCl_3$, in which solvent the spectrum was recorded. A complete deuteration of H6 and 12b-CH_2 was observed. Since the doublet H4 in the original 3-MC spectrum in $CDCl_3$ (see above) was transformed into a singlet, it is clear that the H5 exchange also occurred.

Deuteration of 3-MC at the most basic 6 position generates a carbonium ion with charge localized at the complementary 12b position resulting in the specific deuteration of the adjacent methylene group, in analogy with 7,12-DMBA.

For hydrocarbons of lower basicity, e.g., 7-MBA, a similar study is experimentally impossible since the lifetime of the arenonium ion under the same acidic conditions shortens and no protonation can be observed. In most of the cases, however, it was the decomposition of the compound under such severe conditions that hampered the accomplishment of the experiment.

Kinetics of Proton–Deuterium Ion Exchange in Methylbenzanthracenes. The benzanthracene series has been chosen for the well-studied tumorigenic activity of these compounds[13–16] as well as for their interesting and intriguing structure–activity relationship. In this series the carcinogenic activity ranges from borderline with benzanthracene to potent with some methylbenzanthracenes. It is noteworthy that changes in the position of the methyl group can transform an active compound into a totally inactive one and that in different positions some alkyl substituents elicit different levels of activity. For instance, among the 12 monomethylbenzanthracenes only four display carcinogenic activity, i.e., the 7, 6, 8, and 12 substituted, in decreasing order.

In order to evaluate the relative reactivity of anthracene, benzanthracene, monomethyl-, dimethyl-, and trimethylbenzanthracenes, kinetics of deuterium exchange at the most basic positions were determined. After assignment of the protons in the NMR spectrum of the hydrocarbon, the extent of deuteration was calculated from the ratio between the integrated peak areas corresponding to the partially substituted protons and the integrated peak areas corresponding to the nonsubstituted protons. The angular protons were generally chosen as the nonsubstituted protons since they are localized separately in a downfield spectral region.

Solutions of 0.0352 and 0.0234 M[17] hydrocarbon were made in CCl_4–CF_3COOD (85:15) and CCl_4–CF_3COOD (50:50), respectively. Aliquots were removed periodically, poured into chilled D_2O, extracted with $CHCl_3$, and dried over sodium sulfate. Each extract was then evaporated, the residue was dissolved in a standard amount of CCl_4, and the NMR spectrum was recorded.

The relative rates of deuteration are summarized in Tables I and II. The basicities of the monomethylbenzanthracenes were previously measured by means of competitive extraction experiments[18,19] where the hydrocarbon competed for a limited amount of acid. In the monomethylbenzanthracene series, presented in Table II, 7-MBA and 12-MBA showed the most reactive meso-anthracenic positions. In 6- and 8-MBA the higher reactivity of the 7 position with respect to the corresponding position in BA is caused by the release of steric crowding between the methyl group and the adjacent hydrogen at the 7 position (peri effect)[18] in the tetrahedral conjugated acid. A similar effect on C-12 by the 11-methyl substituent is observed in 11-MBA. The reactivity of the 7 and 12 position in 2-MBA remains unchanged compared to BA, while the presence of a methyl group in the 5 position increased the reactivity of C-7 in 5-MBA.

Nearly all the dimethylbenzanthracenes studied are very potent carcinogens,[16] including the well-known 7,12-DMBA. The addition of a methyl group in the 6 or 8 position of 7-MBA doubles the rate of deuteration on C-12 (Table I). This observation is very curious in view of the fact that the 6- or 8-methyl substituent on BA provide no acceleration whatsoever on C-12. This effect is further increased 30 times when the methyl groups in 7 and 8 positions form a five-membered ring, as in 3-MC.[12] It seems likely that most of this rate enhancement can be attributed to increased hyperconjugative stabilization of the 3-MC arenonium ion resulting from the quasi-coplanarity of the C_1–H bonds and the p orbitals of the aromatic ring. Since canonical forms of 6-protonated 3-MC, in which the positive charge is localized at C-3, cannot be written, it is not reasonable to attribute a major portion of this rate enhancement to the additional 3-methyl substituent.

In 6,12-DMBA and 8,12-DMBA C-7 shows about twice the reactivity as in 12-MBA (Table II). The 7,12-DMBA is characterized by steric repulsion between the 12-CH_3 and the

TABLE I RATES OF DEUTERODEPROTONATION IN CCl_4 - CF_3COOD (85:15) AT 23 ± 1° C

HYDROCARBON	POSITION OF SUBSTITUTION	REACTION TIME (MIN.) 0.5	1	1.5	2	15	20	30	45	60	90	120	180	240	360	480	960	1680	2340	3660
ANTHRACENE	9						0.05			0.07	0.11	0.13		0.24						
	10						0.05			0.07	0.11	0.13		0.24						
BA	7															0.12	0.20	0.45	0.52	0.71
	12															0.09	0.18	0.43	0.50	0.69
7-MBA	12					0.19		0.31	0.43	0.50	0.65	0.86								
12-MBA	7							0.33	0.45	0.52	0.65	0.90								
6,7-DMBA	12					0.37		0.55												
7,8-DMBA	12					0.50		0.68												
8,12-DMBA	7					0.36		0.58												
7,12-DMBA	7-CH_3							0.36		0.73		1.41		2.07	2.52	2.79				
3-MC	5									0.28		0.48	0.59							
	6	0.50	0.75	0.86	0.91															
	12b -CH_2									0.39		0.70	0.89	1.11	1.30	1.45				
6,7,12-TMBA	7-CH_3							1.19				2.26								
	12-CH_3							1.50				2.58								
6,8,12-TMBA	7					0.50		0.68												

TABLE II RATES OF DEUTERODEPROTONATION IN CCl_4 - CF_3COOD (50:50) AT 23 ± 1° C

HYDROCARBON	POSITION OF SUBSTITUTION	REACTION TIME (MIN.) 1	2.5	5	10	20	30	45	60	90	120	180	240	360	480
ANTHRACENE	9				0.19	0.31	0.42								
	10				0.19	0.31	0.42								
BA	7						0.32		0.50			0.77	0.83	0.93	
	12						0.32		0.50			0.76	0.82	0.92	
2-MBA	7						0.36	0.51	0.63	0.78	0.86				
	12						0.31	0.45	0.56	0.73	0.82				
5-MBA	7				0.39		0.79	0.90	1.00						
	12				0.14		0.36	0.51	0.62	0.77	0.85				
6-MBA	7				0.22		0.44	0.55	0.71	0.82	0.89				
	12				0.16		0.28	0.39	0.50	0.62	0.71				
7-MBA	12		0.39	0.56	0.79										
8-MBA	7				0.22		0.45	0.57	0.68						
	12				0.17		0.33	0.43	0.52						
11-MBA	7				0.14		0.33	0.45	0.54	0.67	0.75				
	12				0.25		0.44	0.55	0.65	0.77	0.85				
12-MBA	7		0.38	0.57	0.81										
6,7-DMBA	5												1.00		
	12	0.38	0.77												
	7-CH_3												0.17		0.29
6,12-DMBA	7	0.41	0.74	0.92											
8,12-DMBA	7	0.41	0.71	0.91											
7,12-DMBA	7-CH_3				0.61	1.21	1.66		2.40						
3-MC	5			0.28	0.45	0.68									
	12b -CH_2			0.26	0.42	0.68	1.00								
6,8,12-TMBA	5												1.00		
	7	0.58	0.79												
	12-CH_3												0.27		0.43

hydrogen at C-1. Release of the strain upon protonation at C-12 renders this position the most basic. This effect can be visualized by the selective deuteration of the 7-CH_3 group (Table I), which occurs twice as fast as in the corresponding 12b-CH_2 of 3-MC. Finally, the steric crowding between the 6- and 7-methyl group in 6,7,12-TMBA renders C-7 more basic than C-12 (Table I), as can be observed by the relative deuteration of the methyl groups substituted at the positions complementary to the points of electrophilic attack.

Conclusion

This investigation has primarily revealed that charge lo-

calization in the carbonium ion of 7,12-DMBA, 3-MC, and 6,7,12-TMBA renders this intermediate chemically reactive on the methyl group(s) attached to the carbon atoms at which the charge is localized. Unfortunately, under the acidic conditions sufficiently mild to avoid decomposition, no exchange of the methyl group of other hydrocarbons could be observed. Nevertheless, from the kinetic study of deuterium ion exchange in the methylbenzanthracene series it can be inferred that a general mechanism of hydrocarbon activation by attack of the enzymically catalyzed oxygen species at the most reactive substituting positions with simultaneous formation of electrophilic centers at positions complementary to the points of activation[7] seems to be rather unlikely.

It will be seen in the accompanying paper how the one-electron oxidation of the hydrocarbon, which represents a more plausible mechanism of biological activation, generates radical cations with a significant degree of positive charge localization. Such an effect plays a decisive role in determining the reactivity toward nucleophilic trapping of these intermediates.

Acknowledgments. We wish to express our thanks to Dr. Melvin Newman for the monomethylbenzanthracene compounds and Dr. John Pataki for the dimethylbenzanthracene and trimethylbenzanthracene samples. The valuable comments of Dr. Robert Roth are much appreciated. The financial support of the Cancer Research Funds of the University of California, Berkeley, of the U.S. Atomic Energy Commission, and of the NCI-NIH PH-43-68-959 contract are gratefully acknowledged.

Registry No.—Anthracene, 120-12-7; BA, 56-55-3; 7-MBA, 2541-69-7; 12-MBA, 2422-79-9; 6,7-DMBA, 20627-28-5; 7,8-DMBA, 604-81-9; 8,12-DMBA, 20627-31-0; 7,12-DMBA, 57-97-6; 3-MC, 56-49-5; 6,7,12-TMBA, 20627-33-2; 6,8,12-TMBA, 20627-34-3; 2-MBA, 2498-76-2; 5-MBA, 2319-96-2; 6-MBA, 316-14-3; 8-MBA, 2381-31-9; 11-MBA, 6111-78-0; 6,12-DMBA, 568-81-0; 7,12-DMBA$^+$, 59230-87-4; 7,12-DMBA$^+$-d_4, 59230-88-5; 7,12-DMBA-d_3, 59230-67-0; 3-MC$^+$, 59230-89-6; 3-MC-d_2, 59230-90-9.

Supplementary Material Available. The 220-MHz proton NMR spectra of 7,12-DMBA and 3-MC in different solvent systems (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) J. A. Miller, *Cancer Res.*, **30**, 559–576 (1970).
(2) J. A. Miller, and E. C. Miller, *J. Natl. Cancer Inst.*, **47**, 5–14 (1971).
(3) P. L. Grover, and P. Sims, *Biochem. J.*, **110**, 159–160 (1968).
(4) H. V. Gelboin, *Cancer Res.*, **29**, 1272–1276 (1969).
(5) V. Ullrich, *Angew. Chem., Int. Ed. Engl.*, **11**, 702–712 (1972).
(6) G. A. Hamilton, "Molecular Mechanism of Oxygen Activation", O. Hayaishi, Ed., Academic Press, New York, N.Y., 1974, pp 405–451.
(7) E. Cavalieri and M. Calvin, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 1251–1253 (1971).
(8) C. MacLean, J. H. van der Waals, and E. L. Mackor, *Mol. Phys.*, **1**, 247–256 (1958).
(9) L. K. Keefer, L. Wallcave, J. Loo, and R. S. Peterson, *Anal. Chem.*, **43**, 1411–1416 (1971).
(10) T. J. Batterham, L. Tsai, and H. Ziffer, *Aust. J. Chem.*, **18**, 1959–1966 (1965).
(11) (a) R. H. Martin, *Tetrahedron*, **20**, 897–902 (1964); (b) R. H. Martin, N. Defay, F. Geerts-Evrard, and S. Delavarenne, *Tetrahedron*, **20**, 1073–1090 (1964).
(12) In the 3-MC nomenclature C-6, C-7, 12b-CH_2, and 2a-CH_2 correspond to C-12, C-1, 7-CH_3, and 8-CH_3 in the benzanthracene series, respectively.
(13) W. F. Dunning and M. R. Curtis, *J. Natl. Cancer Inst.*, **25**, 387–391 (1960).
(14) J. L. Stevenson and E. Von Haam, *Am. Ind. Hyg. Assoc. J.*, **26**, 475–478 (1965).
(15) C. B. Huggins, J. Pataki, and R. G. Harvey, *Proc. Natl. Acad. Sci. U.S.A.*, **58**, 2253–2260 (1967).
(16) J. Pataki and C. Huggins, *Cancer Res.*, **29**, 506–509 (1969).
(17) Anthracene and 3-MC were 0.0117 M in CCl_4–CF_3COOD (50:50).
(18) E. L. Mackor, G. Dallinga, J. H. Kruizinga, and A. Hofstra, *Recl. Trav. Chim. Pays-Bas*, **75**, 836–844 (1956).
(19) D. M. Brouwer, E. L. Mackor, and C. MacLean, "Carbonium Ions", Vol. II, G. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., 1970, pp 852–853.

Reaction of Methylbenzanthracenes and Pyridine by One-Electron Oxidation. A Model for Metabolic Activation and Binding of Carcinogenic Aromatic Hydrocarbons

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A simple procedure for generation and trapping of polycyclic aromatic hydrocarbon radical cations in homogeneous solutions of pyridine and iodine is described. Radical cations of benz[*a*]anthracene and its alkyl derivatives are trapped by nucleophilic attack of pyridine on the aromatic nucleus in the order C-7 > C-12 > C-5. When positions 7 or 7 and 12 are blocked by a methyl group, pyridine substitution on the alkyl group competes with ring substitution. Mechanisms for the two types of substitution are proposed and trapping specificity is discussed in terms of charge density and steric factors in the radical ions.

Recently, there has been increasing speculation that radical cations might be the critical intermediates in carcinogenesis by polycyclic aromatic hydrocarbons. Following the original suggestion by Wilk[1] that these intermediates might be important, the conversion of aromatic hydrocarbons to carcinogenic metabolites via one-electron oxidation was demonstrated.[2] More recently Wilk and Girke[3] have reported that the benzo[*a*]pyrene (B[*a*]P) radical cation reacts with nucleic acid bases. Based on the capacity of Fe^{3+} to effect one-electron oxidation of aromatic hydrocarbons,[1,4] it was suggested that hexacoordinated Fe^{3+} in the form of cytochrome P-450 present in microsomes[5] and nuclei[6–8] might act as the cellular oxidant.

Despite the potential biological significance, most studies of aromatic hydrocarbon radical cations have been limited to ESR properties or the mechanistic details of electron transfer steps. While interest in reactions of radical cations with nucleophiles has increased, factors governing the site of nucleophilic attack have received little attention. Among biologically interesting molecules, well-characterized products from nucleophiles and radical cations have been reported only for B[*a*]P.[4,9–11] We have therefore undertaken a study of nu-

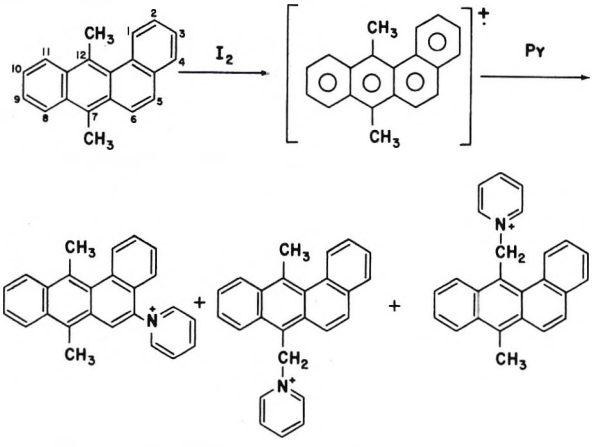
cleophilic trapping of radical cations derived from carcinogenic and noncarcinogenic benz[a]anthracenes.

The ability of iodine to effect a one-electron oxidation of aromatic hydrocarbons to radical cations is well established. The paramagnetic character of certain solid hydrocarbon–iodine complexes has long been known.[12,13] Recently the direct observation of ESR spectroscopy of radical cations in frozen solutions of iodine and several polycyclic aromatic hydrocarbons was reported.[14] The solid-phase reaction of iodine with B[a]P, 7,12-dimethylbenz[a]anthracene (7,12-DMBA), or 3-methylcholanthrene (3-MC) to give dimeric or oligomeric hydrocarbons[1] identical with those obtained through Fe^{3+} oxidation was interpreted as involving radical cation intermediates. In the case of the two former compounds, addition of pyridine gave pyridinium salts which were postulated to have arisen through nucleophilic trapping of the radical ions.[9] These results are paralleled when the radical cations are generated by anodic oxidation.[10,11]

Results

Generation and Trapping of Radical Cations. In seeking a practical system for generating and trapping aromatic radical cations on a synthetic scale, we were attracted to the system of Rochlitz[9] in which the hydrocarbon and pyridine adsorbed on thin layers of silica gel are exposed to iodine vapor. Initially several hydrocarbons were studied in this system with satisfactory results. After some experimentation, however, it was discovered that these reactions can be carried out in homogenous solutions with substantial improvement in yields and convenience.

Benz[a]anthracene (BA) and its alkyl derivatives, dissolved in pyridine in the presence of a high concentration of iodine, gave moderate to high yields of pyridinium salts which arose through nucleophilic trapping of the intermediate radical cations. The crude salts were quantitatively isolated from solutions containing the unreacted hydrocarbon by selective precipitation with ether and examined directly by NMR spectroscopy. Since an efficient method for the quantitative separation of pyridinium salt mixtures was not available, it was necessary to substitute NMR analysis of the gross mixture. Consequently minor products in some cases might not have been detected. For purification to analytical standards, the isolated iodides were converted to picrate or perchlorate salts. The results of these trapping experiments are summarized in Table I and illustrated below for 7,12-DMBA.



Structure Determinations. In the following discussion NMR chemical shifts are from spectra in Me_2SO solutions and are reported in δ units. No distinction is made between spectra of pyridinium iodides, perchlorates, or picrates, since the nature of the anion had no appreciable effect on chemical shifts or coupling constants. In general, structures of the pyridinium salts are readily evident from analysis of their NMR spectra, aided by comparisons with spectra of the hydrocarbons and the detailed chemical shift assignments for substituted benzanthracenes reported by Batteham et al.[15] In all cases where substitution was on the alkyl side chain, assignments were confirmed by spectral comparisons with authentic specimens.

Table I. Trapping Products of Alkyl Benzanthracene Radical Cations by Pyridine

Hydrocarbon[a]	Position(s) of substitution	Yield, %
BA	7	54
2-MBA	7	83
5-MBA	7	85
6-MBA	7	48
	12	14
7-MBA	7-CH_3	54
	12	23
8-MBA	7	58
	12	14
11-MBA	7	82
12-MBA	7	78
7-ETBA	12	68
7,12-DMBA	5	58
	7-CH_3	18
	12-CH_3	15
3-MC	1	96

[a] Abbreviations: MBA, methylbenz[a]anthracene; ETBA, ethylbenz[a]anthracene; DMBA, dimethylbenz[a]anthracene; 3-MC, 3-methylcholanthrene.

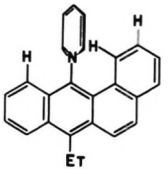
Common features in all spectra are signals arising from the pyridine ring hydrogens. In structures where pyridine is attached directly to the aromatic nucleus, the α protons appear as a doublet of multiplets at 9.5 ± 0.1; the γ proton as a triplet of multiplets at 9.1 ± 0.1; and the β protons as a triplet of multiplets at approximately 8.6. When the pyridine attachment is through an alkyl substituent, the pyridine protons are shifted upfield by approximately 0.5 ppm. The protons of the hydrocarbon nuclei exhibit small to moderate degrees of deshielding in the pyridinium derivatives relative to their parents. An important exception to this generalization is that protons having a peri relationship to the point of pyridine substitution are strongly shielded. This arises from the perpendicular orientation of the pyridine ring with respect to the hydrocarbon ring, and results in positioning of the peri protons within the shielding region of the pyridine ring.

The 100-MHz NMR spectrum of the single pyridinium salt obtained from BA exhibits the following distinctive features: a singlet at 10.02 (1 H), a multiplet at 7.3 (1 H), and a doublet at 7.05 (J = 9 Hz, 1 H). In the NMR spectra of the parent hydrocarbon, the singlet of H12 at 9.4 is at lowest field. The chemical shift of the singlet at 10.02 is most consistent with an assignment to H12 with moderate deshielding by the pyridine substituent at C-7. The multiplets at 7.3 and 7.05 are well upfield from all other protons, requiring that two protons of the hydrocarbon nucleus be simultaneously shielded by the pyridine ring. This could be consistent only with substitution at C-12 or C-7, in which cases the shielded pairs would be H1, H11 or H6, H8, respectively. The fact that the signal at 7.05 is a doublet with no observable long-range coupling strongly implies that it arises from H6, thus establishing substitution at C-7. This assignment is further supported by the observation that H5 and H7 of the structurally related 6-*N*-pyridiniumbenzo[a]pyrenyl perchlorate[4,16] give rise to a nearly identical pattern of chemical shifts and coupling constants. Moreover, the distinctive spectral features arising from substitution at C-12 are described below.

The NMR spectra of the single pyridinium salts obtained from each of the 2-, 11-, and 12-monomethylbenzanthracenes

were very similar, with each containing the characteristic signals of H6 and H8. In the spectrum of 7-*N*-pyridinium-5-MBA, H6 appears as a singlet at 6.9.

The spectrum of the single product obtained from 7-ETBA exhibited the following distinctive features: overlapping multiplets at 7.4–6.9 (2 H), a doublet at 6.19 (J = 8.2 Hz, 1 H), and ethyl group resonances at 3.75 and 1.45. The doublet at 6.19 must arise from an exceptionally strong shielding of a single proton by the pyridine ring. The two protons at 7.4–6.9 are simultaneously shielded to a degree more characteristic of the peri relationship discussed above. These features can only be consistent with substitution at C-12 as shown below.



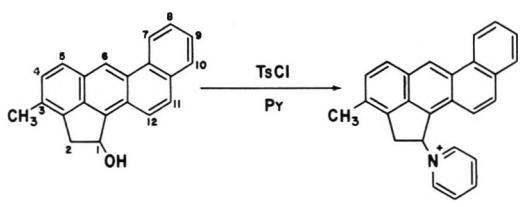
As can be seen in the drawing or more accurately from molecular models, H1 lies well within the shielding region of the pyridine ring and should experience a large upfield shift. The multiplets at 7.4–6.9 arise from H2 and H11, which would also be under the shielding influence of the pyridine ring but farther removed. The only inconsistency with this assignment is that the usual long-range coupling of H3 and H4 to H1 is not observed. This coupling could be reduced, however, by the degree of nonplanarity of the hydrocarbon nucleus induced by the bulky C-12 substituent.

The spectra of product mixtures from 6-MBA and 8-MBA indicated that both the 7-pyridinium and 12-pyridinium salts were present. The spectrum of the mixture from 6-MBA exhibited an abnormally shielded methyl group at 1.87 and a corresponding H8 multiplet at 6.85 for the 7-pyridinium isomer and a methyl singlet and H1 doublet at 2.86 and 6.06, respectively, for the 12-pyridinium isomer.

Likewise the spectrum of products from 8-MBA exhibited the shielded methyl singlet and H6 doublet of the 7 isomer at 1.89 and 6.6, respectively, along with the methyl singlet and H1 doublet of the 12 isomer at 2.92 and 6.1, respectively.

7,12-DMBA gave three trapping products, one of which resulted from ring substitution. The essential features of the NMR spectrum of this compound are a singlet at 8.73 (1 H) and a doublet of multiplets at 7.24 (J = ca. 8 Hz, 1 H), the highest field aromatic signal. These features alone require that the substitution be at C-5, since that position uniquely accounts for both the 8.7 singlet (H6) and the peri shielding of a single proton (H4). In most cases, additional assignment of NMR absorbances could be made by comparison of the hydrocarbon spectrum with that of the pyridinium salt and are reported in the Experimental Section.

The synthesis of authentic pyridinium alkyl benzanthracenes mentioned above involved simple nucleophilic displacement reactions of pyridine with the appropriate bromomethyl derivative. In the case of 3-MC, the tosyl ester, generated by the usual reaction of tosyl chloride with 1-hydroxy-3-methylcholanthrene in pyridine solution, underwent an in situ displacement reaction with pyridine resulting in a one-step synthesis of the desired pyridinium salt:



Discussion

Mechanisms of Radical Cation Trapping. It is to be expected that nucleophilic trapping of an aromatic cation radical should be governed by two main factors: (1) charge distribution in the radical ion and (2) the steric environment of centers on which the charge is preferentially localized. The fact that the benzanthracene radical cation is trapped exclusively at position 7 suggests that the greatest charge density exists at the site. Introduction of an alkyl substituent on the polycyclic nucleus should not dramatically alter the charge distribution. It is not surprising then that the 2-, 5-, 11-, and 12-monomethylbenzanthracenes, where the steric environment of C-7 is unaltered, also give specific C-7 substitution.

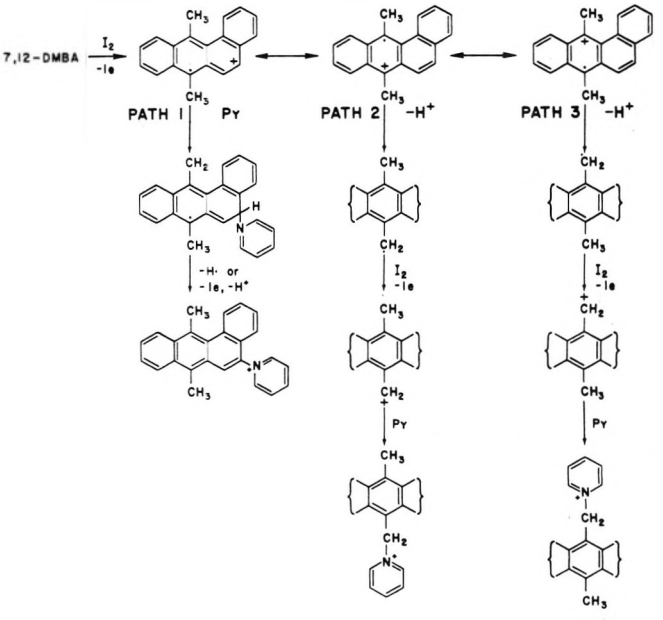
However, when the steric environment about C-7 is restricted and made to resemble more closely the environment inherent at C-12, e.g., by introduction of a methyl substituent at C-6 or C-8, substitution at C-12 begins to compete with that at C-7. This implies that the charge densities at C-7 and C-12 are of comparable magnitude.

When substitution at C-7 and C-12 is blocked, as in 7,12-DMBA, ring substitution proceeds specifically at C-5. Thus the experimental data suggest that the charge density distribution in the BA radical cation decreases in the order 7 > 12 > 5.

These observations are entirely in accord with theoretical calculations[17] which predict the following atomic charge densities in the benz[*a*]anthracene radical cation: C-7, 0.143; C-12, 0.126; C-8, 0.0918; C-5, 0.0904; C-2, 0.0812. Although C-8 is predicted to have slightly greater charge density than C-5, nucleophilic attack at C-8 would be significantly retarded by the steric influence of the 7-methyl substituent.

Introduction of alkyl substituents at C-7 or C-7 and C-12 provides a competitive reaction pathway leading to substitution on the alkyl substituent. The reaction path and proposed mechanism for 7,12-DMBA are illustrated in Scheme I.[18] Removal of one electron from the π system of 7,12-DMBA

Scheme I



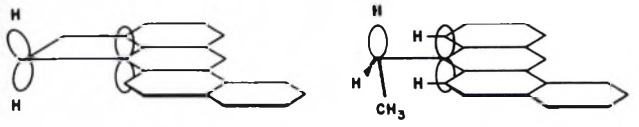
results in a radical ion with the heaviest charge densities at C-7, C-12, C-8, and C-5. With substitution at C-7 and C-12 blocked, and that at C-8 sterically retarded, ring attack proceeds at the position of next highest charge density, C-5 (path 1). The resulting radical can then either lose a hydrogen atom or be oxidized to an arenonium ion with loss of a proton to complete the substitution reaction.

The charge density at C-7 and C-12 is sufficient to induce appreciable acidity in the 7- and 12-methyl hydrogens. Loss of a proton from either group gives a benzylic radical which is rapidly oxidized to a carbonium ion with subsequent trapping by pyridine (path 2 and path 3). The mechanism of formation of pyridinium alkyl derivatives outlined in Scheme I is analogous to that proposed by Andrulis et al.[19] for the formation of anisyl acetate from the *p*-methoxytoluene radical cation. Those workers established from kinetic studies with *p*-methoxytoluene-α,α,α-d_3 that the rate-determining step was loss of a proton from the anisyl ion radical.

It is clear from the results of 7,12-DMBA that the substitution on an alkyl substituent is slow compared to direct attack on the corresponding ring position in the absence of the substituent. This is also apparent in comparing the BA radical ion, which is trapped only at C-7, with the 7-MBA radical ion, which is trapped at C-12 as well as the 7-methyl group.

In the 7-ETBA radical ion, no reaction at the alkyl methylene is observed, and trapping occurs only at C-12. At the other extreme the radical ion of 3-MC is trapped exclusively at the alkyl group. The distribution of substitution between C-12 and the C-7 alkyl substituent (C-1 in 3-MC) among 7-MBA, 7-ETBA, and 3-MC is most likely a reflection of the relative rates of proton loss from the radical ions, since no appreciable differences in charge distribution should exist.

We propose that these differences can be reasonably explained as follows. In 3-MC the C–H bonds of the C-1 methylene are forced into complete alignment with the adjacent aromatic p orbital by geometric constraints. The analogous C–H, p-orbital overlap in 7-ETBA is restricted, primarily by steric repulsion between the methyl group of the ethyl substituent and H6 or H8, and to a lesser extent by H6, or H8 methylene hydrogen repulsion. The situation for 7-MBA is intermediate between these two extremes. As the degree of this overlap decreases, hyperconjugation in the radical ion is minimized, and thus acidity is reduced. A similar argument applies to stabilization of the incipient benzylic radicals. Thus the relative rates of proton loss mentioned above are accounted for by predictable differences, either in hyperconjugation or benzylic radical stabilization.



As the data in this paper illustrate, nucleophilic trapping of aromatic radical ions is indeed controlled by charge distribution and steric factors. However, the potential importance of a third factor, namely the nucleophilicity of the trapping species, should not be ignored.

Studies of B[*a*]P reported in the literature illustrate this point. The B[*a*]P radical cation generated by chemical[3,4] or electrochemical[11] oxidation is trapped by pyridine specifically at C-6. However, Blackburn and Will[11] reported that the electrochemically generated radical ion is trapped by 1-methylimidazole at a site other than C-6, tentatively assigned as C-1. This difference in specificity can be understood by considering the charge distribution in the B[*a*]P radical cation and the relative nucleophilicities of the trapping reagents. Qualitatively, 1-methylimidazole (pK_a = ca. 7) is a significantly stronger nucleophile than pyridine (pK_a = 5). As the strength of the nucleophile is increased, trapping selectivity would become progressively less sensitive to differences in charge density. The highest calculated atomic charge densities[17] in the B[*a*]P radical cation are C-6, 0.131; C-1, 0.118; C-3, 0.100. These figures correctly predict that C-6 would be the primary trapping site with weaker nucleophiles. However, competitive reactions at C-1 and/or C-3 should be observed with sufficiently strong nucleophiles. Furthermore, attack at C-1 or C-3 is sterically more favorable, since these positions are effected by only one peri hydrogen interaction as compared to two such interactions at C-6.

Experimental Section

Melting points are uncorrected. Infrared spectra were obtained by the KBr disk method on a Beckman IR 9 spectrometer and are recorded in cm^{-1}. Ultraviolet spectra were obtained on a Cary 14 spectrometer, using methanol as the solvent, and are reported in nm. NMR spectra were recorded at 100 MHz on a Varian HA-100 spectrometer or at 80 MHz on a Varian CFT-20 Fourier transform instrument. Chemical shifts are reported in parts per million downfield from an internal Me_4Si standard. Microanalyses were performed by Midwest Microlab, Indianapolis, Ind.

Chemicals. Reagent grade pyridine and iodine were used without further purification. Commercially obtained BA, 7,12-DMBA, and 3-MC were purified by column chromatography on Brinkmann silica gel, using hexane–benzene (9:1) followed by recrystallization from benzene–methanol. 7-MBA was prepared by the method of Wood and Fieser[20] and purified as described as above. Crude 12-MBA obtained by the procedure of Cook et al.[21] was purified by filtration through silica gel, followed by chromatography on a column of magnesium oxide–Celite 545, 2:1 w/w, using hexane–benzene (8:2) as the elutant, and subsequent recrystallization from acetic acid. 7-ETBA was prepared by a new synthetic procedure described below. We are indebted to Professor M. S. Newman of The Ohio State University for supplying samples of 2-, 3-, 6-, 8-, and 11-monomethylbenzanthracenes.

General Procedure for One-Electron Oxidation–Pyridine Coupling. Reaction mixtures were magnetically stirred in Erlenmeyer flasks closed with Teflon-lined screw caps. No effort was made to exclude air. Approximately 0.4 mmol of hydrocarbon and 2.0 g (7.9 mmol) of iodine were dissolved in 2.0 ml of pyridine and kept at 30–35 °C from 20 h. The mixture was then diluted with 70 ml of chloroform and washed with sufficient aqueous sodium thiosulfate to discharge the iodine color. Rapid quantitative separation of the pyridinium salts from any unreacted hydrocarbon was accomplished by dropwise addition of the dried (Na_2SO_4), concentrated chloroform solutions to 50–75 ml of ether with stirring. The yellow salts were collected by suction filtration, and the unreacted hydrocarbons were recovered from the filtrate by removal of the solvent. The crude salts were examined directly by NMR.

Conversion of Pyridinium Iodides to Perchlorates and Picrates. For analytical purposes, it was convenient to convert the iodides to picrates or perchlorates, which in many cases seemed to be more stable and have better recrystallization properties.

Perchlorates. Typically, a solution of 200–300 mg of pyridinium iodide in ca. 20 ml of methanol was gradually added to 10 ml of 70% perchloric acid, with cooling. Perchlorates which did not crystallize spontaneously were precipitated by addition of water. Suitable recrystallization solvents were acetone, methanol, or ethanol–water mixtures.

Picrates. Methanol solutions of pyridinium iodide and picric acid (5% molar excess) were mixed and kept at room temperature for 5 min and then poured into cold water. The crude picrates precipitated as bright yellow solids and were recrystallized from acetone–ethanol.

Benz[*a*]anthracene. From 110 mg (0.482 mmol) of BA, 2.6 g (10.2 mmol) of iodine, and 2.6 ml of pyridine was obtained 113 mg (54%) of 7-*N*-pyridiniumbenz[*a*]anthracene iodide as the sole product. Perchlorate: mp ca. 310 °C (preheated bath), gradual decomposition above 250 °C; ir 3120, 3070, 2930, 1625, 1472, 1356, 1122, 1108, 1095, 1083, 1053, 812, 758, 685, 623 cm^{-1}; uv, λ_{max} (log ϵ) 389 (3.47), 369 (3.81), 353 (3.92), 337 (3.87), 323 (3.74), 303 (4.23), 292 (4.73), 281 (4.74), 274 (4.68); 100-MHz NMR (Me_2SO-d_6) 9.97 (s, 1 H, H12), 9.50 (d of m, J = 7 Hz, 2 H, Hα), 9.12 (m, 2 H, Hγ, H1), 8.75–8.4 (m, 3 H), 8.2–7.6 (m, 6 H), 7.3 (m, 1 H, H8), 7.05 (d, J = 10 Hz, 1 H, H6).

Anal. ($C_{23}H_{16}ClNO_4$) C, H, Cl, N.

7-Ethylbenz[*a*]anthracene. From 400 mg (1.56 mmol) of 7-ETBA, 10.0 g (39.4 mmol) of iodine, and 10.0 ml of pyridine was obtained 491 mg (68%) of 7-ethyl-12-*N*-pyridiniumbenz[*a*]anthracene iodide as the only product. The perchlorate had the following properties: mp 123–125 °C; ir 3118, 3073, 2980, 2940, 1627, 1475, 1370, 1150, 1120, 1108, 1095, 1082, 823, 772, 690, 625 cm^{-1}; uv λ_{max} (log ϵ) 398 (3.56), 374 (3.73), 3.60 (3.88), 348 (3.86), 338 (3.72), 292 (4.74), 282 (3.86), 272 (4.71), 262 (4.62), 233 (4.48); 80-MHz NMR (Me_2SO-d_6) 9.56 (d of m, J = 7 Hz, 2 H, Hα), 9.16 (t of m, J = 8 Hz, 1 H, Hγ),

8.8–8.2 (m, 4 H), 8.15–7.48 (m, 5 H), 7.42–6.92 (m, 2 H, H2, H11), 6.19 (d, J = 9 Hz, 1 H, H1), 3.8 (q, J = 7.8 Hz, 2 H, CH_2CH_3), 1.47 (t, J = 7.8 Hz, 3 H, CH_2CH_3).

Anal. ($C_{25}H_{20}ClNO_4$) C, H, Cl, N.

7-Methylbenz[*a*]anthracene. From 123 mg (0.508 mmol) of 7-MBA, 2.6 g (10.2 mmol) of iodine, and 2.6 ml of pyridine was obtained 174 mg (77% total) of a mixture consisting of 7-*N*-pyridiniummethylbenz[*a*]anthracene and 7-methyl-12-*N*-pyridiniumbenz[*a*]anthracene in a 2.4:1 ratio. The relative amounts of the two isomers was determined from the integrated NMR spectrum of the mixture by comparing the area of the H12 singlet of 7-*N*-pyridiniummethylbenz[*a*]anthracene at 9.8 with that of the H1 doublet of 7-methyl-12-*N*-pyridiniumbenz[*a*]anthracene at 6.2. After conversion of the mixture to the perchlorates and fractional recrystallization from 95% ethanol, a pure sample of 7-*N*-pyridiniummethylbenz[*a*]anthracene perchlorate having a melting point and spectral properties identical with those of a synthetic specimen was obtained.

2-Methylbenz[*a*]anthracene. From 72.0 mg (0.297 mmol) of 2-MBA, 2.1 g (8.26 mmol) of iodine, and 2.1 ml of pyridine was obtained 111 mg (83%) of 2-methyl-7-*N*-pyridiniumbenz[*a*]anthracene iodide as the sole product: 80-MHz NMR (Me_2SO-d_6) 9.92 (s, 1 H, H12), 9.45 (d of m, J = 6 Hz, 2 H, Hα), 9.08 (t of m, J = 8 Hz, 1 H, Hγ), 8.95 (s, 1 H, H1), 8.7–8.3 (m, 3 H, Hβ, H11), 8.05–7.4 (m, H3, H4, H5, H9, H10), (m, 1 H, H8), 6.9 (d, J = 9.4 Hz, H6), 2.65 (s, 3 H, CH_3).

5-Methylbenz[*a*]anthracene. From 85.0 mg (0.351 mmol) of 5-MBA, 2.1 g (8.3 mmol) of iodine, and 2.1 ml of pyridine was obtained 133 mg (85%) of 5-methyl-7-*N*-pyridiniumbenz[*a*]anthracene iodide as the only product: 80-MHz NMR (Me_2SO-d_6) 9.88 (s, 1 H, H12), 9.45 (d of m, J = 6 Hz, 2 H, Hα), 9.15 (m, 2 H, H1, Hγ), 8.8–8.3 (m, 3 H), 8.1 (m, 1 H), 7.95–7.5 (m, 4 H), 7.2 (m, 1 H, H8), 6.9 (s, 1 H, H6), 2.6 (s, 3 H, CH_3).

6-Methylbenz[*a*]anthracene. From 100 mg (0.413 mmol) of 6-MBA, 2.6 g (10.2 mmol) of iodine, and 2.6 ml of pyridine was obtained 114 mg (62% total) of a mixture of 6-methyl-7-*N*-pyridiniumbenz[*a*]anthracene and 6-methyl-12-*N*-pyridiniumbenz[*a*]anthracene in a 3.5:1 ratio. The relative abundance of the two isomers was determined from the integrated NMR spectrum of the mixture by comparing the methyl singlets at 1.85 (6-methyl-7-*N*-pyridinium) and 2.85 (6-methyl-12-*N*-pyridinium). The H8 multiplet of the 6-methyl-7-*N*-pyridinium isomer was observed at 6.85 and the H1 doublet (J = 9 Hz) of the 6-methyl-12-*N*-pyridinium isomer at 6.1. The remainder of the NMR spectrum was unexceptional and consistent with the assigned structures.

8-Methylbenz[*a*]anthracene. From 110 mg (0.454 mmol) of 8-MBA, 2.6 g (10.2 mmol) of iodine, and 2.6 ml of pyridine was obtained 147 mg (72% total) of a mixture of 7-*N*-pyridinium-8-methylbenz[*a*]anthracene and 8-methyl-12-*N*-pyridiniumbenz[*a*]anthracene iodides in a ratio of 4.3:1. The relative abundance of the two isomers was determined from the integrated NMR spectrum of the mixture by comparing the methyl singlets at 1.89 (7-*N*-pyridinium) and 2.92 (12-*N*-pyridinium). The H6 doublet of the 7-pyridinium isomer appears at 6.6 (J = 9.6 Hz), while the H1 doublet of the 12-pyridinium isomer appears at 6.1 (J = 9 Hz). The remainder of the spectrum is unexceptional and consistent with the assigned structures.

11-Methylbenz[*a*]anthracene. From 92.0 mg (0.380 mmol) of 11-MBA, 2.7 g (10.6 mmol) of iodine, and 2.7 ml of pyridine was obtained 138 mg (82%) of 7-*N*-pyridinium-11-methylbenz[*a*]anthracene iodide as the only product: 80-MHz NMR (Me_2SO-d_6) 9.73 (s, 1 H, H12), 9.4 (d, J = 6 Hz, 2 H, Hγ), 9.14 (t of m, J = 8 Hz, 2 H, Hγ, H1), 8.6 (t of m, J = 6.6 Hz, 2 H, Hβ), 8.1–7.4 (m, 6 H, H2, H3, H4, H5, H9, H10), 7.0 (d, J = 9 Hz superimposed on a multiplet 2 H, H6, H8), 3.0 (s, 3 H, CH_3).

12-Methylbenz[*a*]anthracene. From 229 mg (0.946 mmol) of 12-MBA, 5.00 g (19.7 mmol) of iodine, and 5.0 ml of pyridine was obtained 332 mg (78%) of 7-*N*-pyridinium-12-methylbenz[*a*]anthracene iodide as the only detectable product. The perchlorate had the following properties: mp >260 °C dec; ir 3123, 3080, 1628, 1477, 1382, 1372, 1148, 1125, 1097, 1059, 870, 768, 688, 625 cm^{-1}; uv λ_{max} (log ϵ) 394 (3.37), 374 (3.77), 360 (3.88), 346 (3.80), 305 (4.22), 294 (4.53), 278 (4.66), 222 (4.52); 80-MHz NMR (Me_2SO-d_6) 9.4 (d of m, J = 7 Hz, 2 H, Hα), 9.05 (t of m, J = 7.5 Hz, 1 H, Hγ), 8.8–8.3 (m, 4 H), 8.2–7.5 (m, 6 H), 7.2 (m, 1 H, H8), 6.85 (d, J = 9.9 Hz, 1 H, H6), 3.48 (s, 3 H, CH_3).

7,12-Dimethylbenz[*a*]anthracene. From 100 mg (0.391 mmol) of 7,12-DMBA, 2.0 g (7.9 mmol) of iodine, and 2.0 ml of pyridine was obtained 164 mg (91% total) of a mixture consisting of 64% 5-*N*-pyridinium-7,12-dimethylbenz[*a*]anthracene iodide, 20% 7-*N*-pyridiniummethyl-12-methylbenz[*a*]anthracene iodide, and 16% 7-methyl-12-*N*-pyridiniummethylbenz[*a*]anthracene iodide. The relative abundance of the three isomers was determined from the integrated NMR spectrum of the mixture by comparing the signals of 5-*N*-pyridinium-7,12-DMBA at 9.5 (Hα) and 7.2 (H4) with the methylene singlets of the 12-pyridiniummethyl and 7-pyridiniummethyl isomers at 7.06 and 6.95, respectively.

A mixture of the three salts (975 mg) was dissolved in a minimum volume of methylene chloride and diluted with 40 ml of acetone, whereupon the 5-pyridinium isomer selectively precipitated. The mother liquor was evaporated, and the residue was redissolved in the minimal volume of methylene chloride. After dilution with acetone as before, the 7-pyridiniummethyl isomer gradually crystallized with only minor amounts of isomeric contaminants. The mother liquor from the second crystallization contained the 12-pyridiniummethyl isomer as the chief component along with significant amounts of the two other isomers. Each of the three isomers was obtained in pure form after treatment of the fractions with perchloric or picric acid and recrystallization. The 7-pyridiniummethyl and 12-pyridiniummethyl picrates had melting points, ir, and NMR spectra identical with those of their synthetic counterparts. 5-*N*-Pyridinium-7,12-dimethylbenz[*a*]anthracene perchlorate had the following properties: mp 256–257 °C (lit.[9] 248–250 °C); ir 3120, 3070, 1622, 1470, 1120, 1110, 1090, 772, 760, 690, 685, 635, 623 cm^{-1}; uv λ_{max} (log ϵ) 405 (3.49), 366 (3.83), 300 (4.69), 290 (4.68), 279 (4.50), 256 (4.48), 234 (4.36); 100-MHz NMR (Me_2SO-d_6), 9.5 (d of m, J = 7 Hz, 2 H, Hα), 8.97 (t of m, J = 8 Hz, 1 H, Hγ), 8.73 (s, 1 H, H6), 8.6 (d of m, J = 8 Hz, 1 H, H1), 8.68–8.35 (m, 4 H, Hβ, H8, H11), 7.95–7.5 (m, 4 H, H2, H3, H9, H10), 7.24 (d of m, J = 8 Hz, 1 H, H4), 3.3 (s, 3 H, 12-CH_3), 3.1 (s, 3 H, 7-CH_3).

Anal. ($C_{25}H_{20}ClNO_4$) C, H, Cl, N.

3-Methylcholanthrene. From 112 mg (0.418 mmol) of 3-MC, 3.6 g (14.2 mmol) of iodine, and 3.6 ml of pyridine was obtained 190 mg (96%) of 1-*N*-pyridinium-3-methylcholanthrene iodide. The perchlorate had ir, uv, and NMR spectral properties identical with those of the synthetic specimen described below.

7-*N*-Pyridiniummethyl-12-methylbenz[*a*]anthracene Picrate. 7-Hydroxymethyl-12-methylbenz[*a*]anthracene was prepared by the method of Boyland and Sims.[22] A solution of 500 mg (1.85 mmol) of phosphorus tribromide in 4 ml of benzene was added over 5 min to a well-stirred suspension of 240 mg (0.904 mmol) of 7-hydroxymethyl-12-methylbenz[*a*]anthracene in 15 ml of benzene. After 1.5 h at room temperature, the reaction mixture was poured into 20 ml of water. The benzene layer was washed with saturated sodium bicarbonate solution and water, dried ($MgSO_4$), and evaporated to give 288 mg (96%) of crude 7-bromomethyl-12-methylbenz[*a*]anthracene: 100-MHz NMR ($CDCl_3$) 8.4–8.15 (m, 3 H), 7.86 (d, J = 9 Hz, 1 H), 7.8–7.3 (m, 6 H), 5.32 (s, 2 H, CH_2Br), 3.19 (s, 3 H, CH_3).

The crude bromomethyl-12-MBA (60 mg) was dissolved in 6 ml of pyridine. 7-Pyridiniummethyl-12-MBA bromide began to precipitate within minutes. After 2 h at room temperature, ether was added to complete the precipitation, and the product was collected, yield 73 mg (98%). The bromide was converted to the title picrate by the usual procedure: mp 178–179 °C; ir 3080, 1630, 1610, 1550, 1490, 1475, 1433, 1363, 1332, 1310, 1290, 1263, 1160, 1140, 1075, 920, 908, 818, 785, 750, 705, 678 cm^{-1}; uv λ_{max} (log ϵ) 363 (4.35), 348 (4.33), 295 (4.80), 284 (4.79), 275 (4.63), 260 (4.62); 100-MHz NMR (Me_2SO-d_6) 8.92 (d of m, J = 7 Hz, 2 H, Hα), 8.75–8.3 (m, 6 H, includes picrate hydrogen singlet at 8.55), 8.3–7.5 (m, 9 H), 6.95 (s, 2 H, CH_2N), 3.35 (s, 3 H, CH_3).

Anal. ($C_{31}H_{22}N_4O_7$) C, H, N.

7-Methyl-12-*N*-pyridiniummethylbenz[*a*]anthracene Picrate. The synthesis described is analogous to that employed for the 7-pyridiniummethyl isomer. However, since the synthesis of 12-hydroxymethyl-7-methylbenz[*a*]anthracene via the lead tetraacetate oxidation of DMBA gives the 12-hydroxymethyl isomer in low yield,[22] a more efficient method of synthesis was sought. A mixture of 3.00 g (11.7 mmol) of 7,12-DMBA and 2.115 g (11.9 mmol) of *N*-bromosuccinimide in 60 ml of carbon tetrachloride was heated to reflux and irradiated with a sunlamp for 15 min. After removal of the succinimide and solvent, 4.0 g of solid residue was obtained. NMR analysis indicated a molar composition of 55% 12-bromomethyl-7-MBA (singlets at 2.66 and 5.24), 30% 7-bromomethyl-12-MBA (singlets at 2.94 and 5.08), and 15% unreacted DMBA (singlets at 2.76 and 3.10). The crude mixture, 1.33 g, was dissolved in 20 ml of tetrahydrofuran, mixed with 3 ml of 2 N sodium hydroxide solution, and stirred at room temperature for 40 h. The THF was removed on a rotary evaporator, and the residue was dissolved in benzene. After washing with water, drying ($MgSO_4$), and evaporating the solvent, 1.19 g of residue were obtained. Analysis of the residue by TLC confirmed the presence of the two isomeric alcohols and DMBA. Chromatography on an alumina column with benzene afforded 265 mg of pure 12-hydroxymethyl-7-methylbenzanthracene. A sample recrys-

tallized from ethanol melted at 264 °C (lit.[22] 264 °C). Reaction of the alcohol with phosphorus tribromide under the conditions described for 7-hydroxymethyl-12-MBA gave 12-bromomethyl-7-MBA in 85% yield: 100-MHz NMR ($CDCl_3$) 8.95 (m, 1 H), 8.49 (m, 1 H), 8.10 (m, 1 H), 7.75–7.2 (m, 7 H), 5.32 (s, 2 H, CH_2Br), 2.76 (s, 3 H, CH_3). The bromomethyl derivative was converted by the usual procedure to the title picrate: mp 164–165 °C dec; ir 3120, 3080, 1631, 1610, 1552, 1495, 1478, 1435, 1363, 1335, 1311, 1290, 1270, 1160, 1138, 1075, 785, 745, 708, 680 cm^{-1}; uv λ_{max} (log ϵ) 400 (4.08), 381 (4.22), 363 (4.32), 352 (4.31), 297 (4.76), 286 (4.77), 275 (4.61), 266 (4.56), 237 (4.51); 100-MHz NMR (Me_2SO-d_6) 8.88 (m, 2 H, Hα), 8.75–8.35 (m, 4 H, includes picrate hydrogen singlet at 8.55), 8.35–7.35 (m, 11 H), 7.06 (s, 2 H, CH_2N), 3.15 (s, 3 H, CH_3).

Anal. ($C_{31}H_{22}N_4O_7$) C, H, N.

7-*N*-Pyridiniummethylbenz[*a*]anthracene Perchlorate. 7-Bromomethylbenz[*a*]anthracene was prepared from BA by the bromomethylation procedure of Dipple and Slade[23] and converted to the title perchlorate by a procedure analogous to that described for the pyridiniummethylmethylbenz[*a*] anthracenes. The title compound exhibited the following properties: mp 212–213 °C; ir 3120, 3050, 1625, 1497, 1478, 1142, 1121, 1108, 1090, 1053, 830, 767, 755, 694, 683, 675, 622 cm^{-1}; uv λ_{max} (log ϵ) 390 (3.47), 372 (3.85), 356 (3.96), 341 (3.86), 326 (3.67) 292 (4.91), 281 (4.83), 271 (4.59), 254 (4.48), 230 (4.51); 100-MHz NMR (acetone-d_6) 9.62 (s, 1 H, H12), 8.98 (d of m, J = 7 Hz, 3 H, Hα, H1), 8.62 (t of m, J = 8 Hz, Hγ), 8.5–7.5 (m, 11 H), 7.05 (s, 2 H, CH_2N).

Anal. ($C_{24}H_{18}ClNO_4$) C, H, Cl, N.

1-*N*-Pyridinium-3-methylcholanthrene Perchlorate. A solution of 800 mg (2.62 mmol) of 1-hydroxy-3-methylcholanthrene[24] and 1.075 g (5.64 mmol) of *p*-toluenesulfonyl chloride in 25 ml of pyridine was kept at −4 °C for 3 days. The mixture was then diluted with 75 ml of cold water. After 20 min, the crude 1-*N*-pyridinium-3-MC tosylate was collected and dried by suction filtration. The tosylate was purified by dissolution in 50 ml of hot chloroform and addition of ether to the cooled solution to complete the precipitation. The tosylate was converted quantitatively to the perchlorate as described in the general procedure: mp <260 °C dec; ir 3060, 1628, 1495, 1482, 1120, 1108, 1090, 825, 795, 772, 750, 680, 635, 622 cm^{-1}; uv, λ_{max} (log ϵ) 393 (3.15), 375 (3.76), 358 (3.91), 341 (3.83), 327 (3.66), 295 (4.86), 283 (4.82), 273 (4.61), 233 (4.47), 222 (4.57); 100-MHz NMR (Me_2SO-d_6), 9.58 (s, 1 H, H6), 9.16–8.84 (m, 3 H, Hα, H7), 8.62 (t of m, J = 8 Hz, 1 H, Hγ), 8.3–7.4 (m, 10 H), 4.36 (d of d, J = 19 and 8 Hz, 1 H, H2), 3.76 (d, J = 19 Hz, 1 H, H2′), 2.46 (s, 3 H, CH_3).

Anal. ($C_{26}H_{20}ClNO_4$) C, H, Cl, N.

Synthesis of 7-Ethylbenz[*a*]anthracene. To a stirred solution of 2.80 g (12.3 mmol) of benz[*a*]anthracene and 5.80 g (73.9 mmol) of acetyl chloride in 20 ml of chloroform maintained at 0 to −5 °C was gradually added 3.30 g (24.7 mmol) of anhydrous aluminum chloride. After 30 min the mixture was allowed to warm to 10 °C, and water was added to decompose the complex. The chloroform layer was removed, and the aqueous layer was extracted with additional portions of chloroform. The combined chloroform solutions were washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on alumina using hexane–benzene 4:1 as the elutant, to give 2.39 g (72%) of 7-acetylbenz[*a*]anthracene: 100-MHz NMR ($CDCl_3$) 8.92 (s, 1 H, H12), 8.55 (m, 1 H, H1), 8.0–7.3 (m, 9 H, 2.64 (s, 3 H, CH_3).

Lithium aluminum hydride (2.25 g, 59.3 mmol) was added to a solution of anhydrous aluminum chloride (15.7 g, 118 mmol) with stirring. After 30 min, solid 7-acetylbenz[*a*]anthracene (4.00 g, 14.8 mmol) was added in sufficiently small portions to keep the solution below reflux temperature. Within 5 min after the final addition, no starting material could be detected by TLC, and the excess $LiAlH_4$ was decomposed by adding ethyl acetate. The mixture was poured into water and extracted with chloroform. From the chloroform extracts was obtained 3.5 g of crude 7-ETBA which was purified by chromatography on a silica gel column using hexane–benzene (9:1) as elutant, and subsequent recrystallization from benzene–methanol: yield 3.3 g (87%); mp 112–113 °C (lit.[25] 113.5–114 °C); 100-MHz NMR ($CDCl_3$) 8.97 (s, 1 H, H12), 8.72 (m, 1 H, H1), 8.20 (m, 1 H), 8.1–7.9 (m, 2 H), 7.85–7.3 (m, 6 H), 3.50 (q, J = 8 Hz, 2 H, CH_2), 1.37 (t, J = 8 Hz, 3 H, CH_3).

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Registry No.—BA, 56-55-3; 2-MBA, 2498-76-2; 5-MBA, 2319-96-2; 6-MBA, 316-14-3; 7-MBA, 2541-69-7; 8-MBA, 2381-31-9; 11-MBA, 6111-78-0; 12-MBA, 2422-79-9; 7-ETBA, 3697-30-1; 7,12-DMBA, 57-97-6; 3-MC, 56-49-5; pyridine, 110-86-1; 7-*N*-pyridiniumbenz[*a*]-anthracene perchlorate, 59230-69-2; 7-ethyl-12-*N*-pyridiniumbenz[*a*]anthracene perchlorate, 59230-71-6; 2-methyl-7-*N*-pyridiniumbenz[*a*]anthracene iodide, 59230-72-7; 5-methyl-7-*N*-pyridiniumbenz[*a*]anthracene iodide, 59230-73-8; 7-*N*-pyridinium-11-methylbenz[*a*]anthracene iodide, 59230-74-9; 7-*N*-pyridinium-12-methylbenz[*a*]anthracene perchlorate, 59230-76-1; 5-*N*-pyridinium-7,12-dimethylbenz[*a*]anthracene perchlorate, 17066-30-7; 7-*N*-pyridiniummethyl-12-methylbenz[*a*]anthracene picrate, 59230-78-3; 7-hydroxymethyl-12-methylbenz[*a*]anthracene, 568-75-2; 7-bromomethyl-12-methylbenz[*a*]anthracene, 16238-56-5; 7-methyl-12-*N*-pyridiniummethylbenz[*a*]anthracene picrate, 59230-80-7; 12-bromomethyl-7-MBA, 59230-81-8; 7-*N*-pyridiniummethylbenz[*a*]anthracene perchlorate, 59230-82-9; 1-*N*-pyridinium-3-methylcholanthrene perchlorate, 59230-84-1; 1-hydroxy-3-methylcholanthrene, 3342-98-1; acetyl chloride, 75-36-5; 7-acetylbenz[*a*]-anthracene, 59230-85-2.

References and Notes

(1) M. Wilk, W. Bez, and J. Rochlitz, *Tetrahedron*, **22**, 2599–2608 (1966).
(2) (a) J. Fried and D. E. Schumm, *J. Am. Chem. Soc.*, **89**, 5508–5509 (1967); (b) J. Fried, "Chemical Carcinogenesis", Part A, P. O. P. Ts'o and J. DiPaolo, Ed., Marcel Dekker, New York, N.Y., 1974, pp 197–215.
(3) M. Wilk and W. Girke, *J. Natl. Cancer Inst.*, **49**, 1585–1597 (1972).
(4) E. Cavalieri and R. Auerbach, *J. Natl. Cancer Inst.*, **53**, 393–397 (1974).
(5) S. Orrenius and L. Ernster, "Molecular Mechanism of Oxygen Activation", O. Hayaishi, Ed., Academic Press, New York, N.Y., 1974, pp 405–451.
(6) A. S. Khandwala and C. B. Kasper, *Biochem. Biophys. Res. Commun.*, **54**, 1241–1246 (1973).
(7) E. G. Rogan and E. Cavalieri, *Biochem. Biophys. Res. Commun.*, **58**, 1119–1126 (1974).
(8) E. G. Rogan, P. Mailander, and E. Cavalieri, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 457–461 (1976).
(9) J. Rochlitz, *Tetrahedron*, **23**, 3043–3048 (1967).
(10) L. Jeftic and R. N. Adams, *J. Am. Chem. Soc.*, **92**, 1332–1337 (1970).
(11) G. M. Blackburn and J. P. Will, *J. Chem. Soc., Chem. Commun.*, 67–68 (1974).
(12) A. Szent-Gyorgyi, I. Isenberg, and S. L. Baird, Jr., *Proc. Natl. Acad. Sci. U.S.A.*, **46**, 1444–1449 (1960).
(13) L. S. Singer and J. Kommandeur, *J. Chem. Phys.*, **34**, 133–140 (1961).
(14) W. Caspary, B. Cohen, S. Lesko, and P. O. P. Ts'o, *Biochemistry*, **12**, 2649–2656 (1973).
(15) T. J. Batterham, L. Tsai, and H. Ziffer, *Aust. J. Chem.*, **18**, 1959–1966 (1965).
(16) M. D. Johnson and M. Calvin, *Nature (London)*, **241**, 271–272 (1973).
(17) Calculations of A. Liakus and G. A. Gallup by an approximate effective core potential method; to be published.
(18) Although Rochlitz[9] studied the reaction of 7,12-DMBA with iodine and pyridine on silica gel, the ring substitution compound 5-*N*-pyridinium-7,12-dimethylbenz[*a*]anthracene perchlorate was the only reported product. We have repeated the reaction on silica gel with results very similar to those obtained in homogenous solution.
(19) P. J. Andrulis, Jr., M. J. S. Dewar, R. Dietz, and R. L. Hunt, *J. Am. Chem. Soc.*, **88**, 5473–5478 (1966).
(20) J. L. Wood and L. F. Fieser, *J. Am. Chem. Soc.*, **62**, 2674–2681 (1940).
(21) J. W. Cook, A. M. Robinson, and F. Goulden, *J. Chem. Soc.*, 393–396 (1937).
(22) E. Boyland and P. Sims, *Biochem. J.*, **95**, 780–787 (1965).
(23) A. Dipple and T. A. Slade, *Eur. J. Cancer*, **6**, 417–423 (1970).
(24) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **60**, 2542–2548 (1938).
(25) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **59**, 1028–1036 (1937).

Chemiluminescence from the Reaction of Singlet Oxygen with 10,10′-Dimethyl-9,9′-biacridylidene. A Reactive 1,2-Dioxetane

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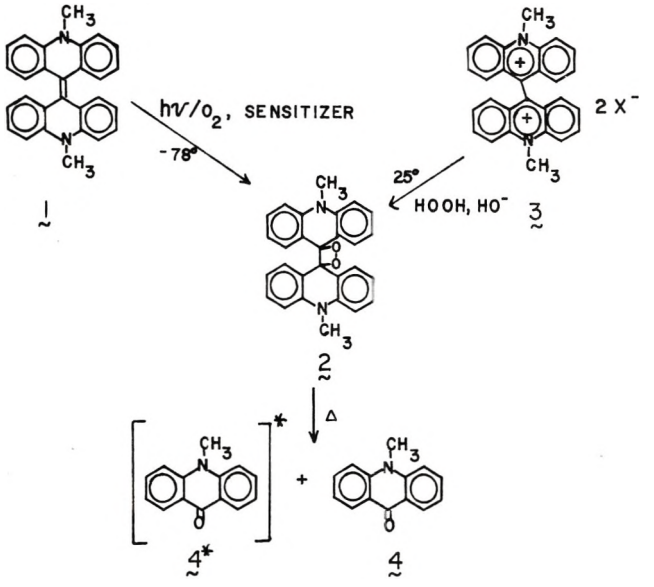
Irradiation of 10,10′-dimethyl-9,9′-biacridylidene (DBA) in several oxygen saturated solvents at −78 °C in the presence of zinc tetraphenylporphine leads to the corresponding 1,2-dioxetane (**2**). While **2** is stable at −78 °C, it decomposes into two molecules of *N*-methylacridone (NMA) at higher temperatures ($\tau_{1/2} \sim 1$ min at 0 °C) with light evolution (NMA fluorescence). The activation parameters have been measured to be dichloromethane, $\Delta H^{\ddagger} = 17.2 \pm 0.3$ kcal/mol, $\Delta S^{\ddagger} = -1.1 \pm 1.1$ eu; benzene, $\Delta H^{\ddagger} = 16.7 \pm 0.2$ kcal/mol, $\Delta S^{\ddagger} = -5.0 \pm 2.1$ eu; pinacolone, $\Delta H^{\ddagger} = 18.2 \pm 0.3$ kcal/mol, $\Delta S^{\ddagger} = -1.4 \pm 1.2$ eu. The chemiexcitation quantum yield for formation of ^{1}NMA* is 0.036 ± 0.018 for the photooxygenation ($\lambda_{excitation} > 550$ nm) or triphenyl phosphite ozonide oxidation of DBA. However, photooxygenation using unfiltered light gives quantum yields lower by a factor of 20 which is ascribed to photoinduced decomposition of **2**. The quantum yield for formation of ^{3}NMA* has been measured as 0.04 ± 0.01.

1,2-Dioxetanes have been recognized as important intermediates in chemiluminescence reactions[2] and in alkene photooxygenations.[3] McCapra and Hann[4] reported chemiluminescence (CL) from reaction of singlet ($^1O_2$) oxygen (from triphenyl phosphite ozonide, $Br_2/H_2O_2/OH^-$, and rf discharge) with 10,10′-dimethyl-9,9′-biacridylidene (DBA, **1**), presumably arising from the thermal decomposition of a 1,2-dioxetane intermediate, **2**. This compound has been proposed as the key intermediate in the "classical" CL reaction of lucigenin (**3**).[5]



We wish to report the successful low-temperature (−78 °C) photosensitized oxygenation of DBA to **2** and a kinetic study of the CL reaction near 0 °C. In addition, a wavelength effect of the photolyzing light on the CL quantum yield (*N*-methylacridone and DBA fluorescence) was noted. For comparison, the CL quantum yield from **2**, produced via reaction of $^1O_2$, generated from decomposition of triphenyl phosphite ozonide ($TPPO_3$), with DBA has been determined. Finally, the quantum yield for formation of *N*-methylacridone triplet from decomposition of **2** has been determined.

Results and Discussion

Photooxygenation of DBA in various solvents at −78 °C is readily accomplished by irradiating an oxygen-saturated solution of DBA (~2×10^{-4} M)[6] with visible light in the presence of zinc tetraphenylporphine (ZnTP) (10^{-4}–10^{-5} M).[7,8] A low-level, self-sensitized reaction is observed in the absence of sensitizer[9] but the sensitizer increases the yield of the reaction by at least two orders of magnitude. Contrary to an earlier report,[4] no CL is observed following reaction at −78 °C while the low temperature is maintained. However, a bright CL is observed as the sample is warmed toward room temperature, which we ascribe to the decomposition of **2** by analogy with similar systems.[3]

Our results confirm previous reports that *N*-methylacridone (NMA, **4**) is the primary emitter in the CL reaction, the emission being NMA fluorescence[4] (see Figure 1). Under conditions of high remaining DBA concentration (i.e., incomplete reaction, DBA ≥ 10^{-4} M), a significant amount of the emission is DBA fluorescence produced via singlet–singlet energy transfer from NMA:[10] ^{1}NMA* + DBA → NMA + ^{1}DBA*. Reaction of DBA with $^1O_2$ produced from the decomposition of $TPPO_3$ gave similar CL spectra.

Kinetics. The rates of thermal decomposition of **2** in several solvents at various temperatures have been determined by directly monitoring the CL decay. After the sample reached thermal equilibrium following warmup from −78 °C, the CL decay was first order out to ca. 3 half-lives. The CL decay is independent of sensitizer concentration over the concentration range used. As a check, methylene blue was used as a sensitizer and gave identical kinetic results. The derived activation parameters appear in Table I.

As previously noted,[11] there is an appreciable effect of trace impurities on the kinetics. Column chromatography over silica gel proved effective in purifying dichloromethane (see Table I). Saturating pyridine with disodium ethylenediaminetetraacetic acid (EDTA) did not prove to be totally effective in eliminating the impurity effect on the kinetics (see Table I).

Note that our kinetic data predict a relatively short lifetime ($\tau_{1/2} \sim 7$ s) for **2** at room temperature which is consistent with it being a short-lived intermediate during the lucigenin/H_2O_2/HO^- reaction.[5] This reactivity of **2** is generally greater than that of many previously reported 1,2-dioxetanes of alkenes,[12–14] but appears comparable to the reactivity reported for 1,2-dioxetanes derived from enamines.[15,16]

Chemiexcitation Quantum Yields. Chemiexcitation quantum yields (see footnote *a*, Table II) of electronically excited singlet state formation, $^1\Phi_{CE}$, were determined by

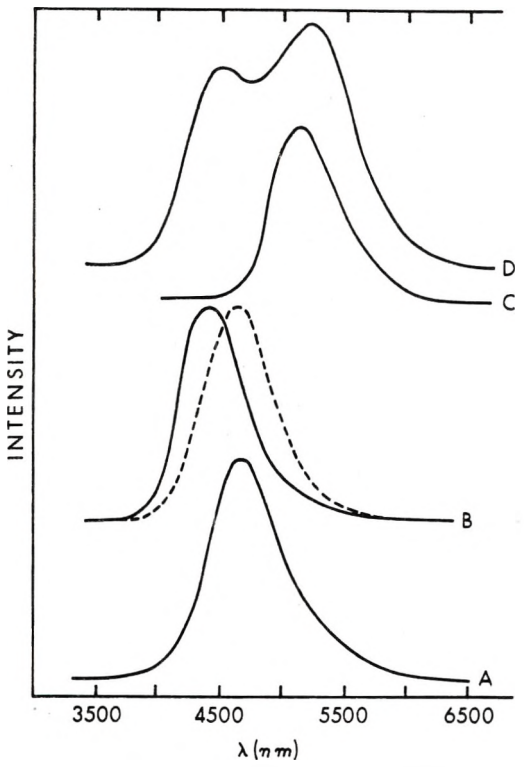


Figure 1. Chemiluminescence during warmup after $^1O_2$ reaction with DBA at −78 °C: (A) normalized fluorescence spectrum of NMA in the absence (B—) and presence (B - - -) of ZnTP (10^{-4} M). Fluorescence spectrum of DBA in the presence (C) of ZnTP (10^{-4} M). Chemiluminescence from incomplete reaction of DBA with $^1O_2$ (D). The shift in (B - - -) is due to internal absorption of high-energy side of emission band by ZnTP.

assaying specific runs for both NMA formed and photons emitted. Product yields were determined from fluorometric assay with known concentrations of NMA as internal standards by the method of standard additions. This technique allows accurate measurement of the NMA concentration after reaction, since any fluorescence quenching that might occur will affect both the unknown and standard equally. Photon yields were photometrically determined relative to the luminol–hemin–H_2O_2 reaction which served as an absolute photon source.[17] Because of the spectral similarity of the CL's from the luminol reaction and decomposition of **2**, a correction for photomultiplier response was not necessary. These yields are shown in Table II. The values of Φ_f for NMA were determined under aerated condition which mimics the situation during the CL reaction.

As a check, the $^1\Phi_{CE}$ for the $TPPO_3$ reaction was measured (Table II). The discrepancy in $^1\Phi_{CE}$ of ca. 20 between the two reactions led to a study of possible complications in the photooxygenation reaction. The lower $^1\Phi_{CE}$ in the latter appears not to be due to the presence of the sensitizer since the CL kinetics are independent of sensitizer concentration and quenching of the NMA fluorescence by the sensitizer under our conditions is negligible. However, we did note *decreasing* relative light yields[18] with *increasing* photolysis time. The self-sensitized photooxygenation reaction showed the same results.

These observations suggested that the reduced light yields in the photooxygenation reactions were a result of the direct photodecomposition of **2** during the photolysis and/or a sensitized decomposition via DBA*. The absorbance of DBA extends to ca. 500 nm and **2** should not absorb at longer wavelengths. Accordingly, a Corning CS 3-67 filter (550 nm short wavelength cutoff) was placed between the light source and the photolysis Dewar. With this filter in place, the relative light yields were found to increase with photolysis time, indicating stability of **2** under these conditions. The $^1\Phi_{CE}$ thus obtained compares favorably (see Table II) with that measured for the $TPPO_3$ reaction and we consider this a good (±50%) estimate of the ^{1}NMA* yield for the decomposition of **2**.

The sensitized *trans* → *cis*-stilbene reaction was used as a probe for counting the ^{3}NMA* yield. Irradiation (366 nm) of an aerated dichloromethane solution of *trans*-stilbene (1.0×10^{-2} M) containing NMA (1.0×10^{-3} M) showed efficient interception of the ^{3}NMA* by *trans*-stilbene with a sensitization quantum efficiency of essentially unity for the trans → cis isomerization (ferrioxalate actinometry, accounting for $\Phi_{ISC} \sim 0.56$ in NMA from $\Phi_{ISC} = 1 - \phi_f$). Singlet–triplet and singlet–singlet energy transfer are ruled out since *trans*-stilbene does not quench the fluorescence of NMA. For the counting experiment, scintillation grade *trans*-stilbene was further purified by preparative gas chromatography yielding a sample containing ≤0.02% *cis*-stilbene. This purified *trans*-stilbene (1.0×10^{-2} M) was added to a dichloromethane solution of DBA–$TPPO_3$ at −78 °C (conditions the same as in the CL quantum yield experiment) and the mixture allowed to warm to room temperature. Gas chromatography indicated an enrichment of the *cis*-stilbene over the starting stilbene mixture.[19] From the *cis*-stilbene yield, we estimate the quantum yield for formation of ^{3}NMA* to be 0.04 ± 0.01, assuming triplet sensitization to be completely efficient.[20] The expected quantum yield for ^{3}NMA* arising from intersystem crossing of ^{1}NMA* alone is 0.02 ± 0.01 ($\Phi_{^3NMA^*} = {}^1\Phi_{CE} \times \Phi_{ISC}$).

In summary, we have found that (1) the kinetics of the decomposition of **2** are relatively solvent independent in aprotic solvents in the absence of impurity effects, (2) the $^1\Phi_{CE}$ is relatively high leading to substantial CL, comparable to the CL from luminol[17] and lucigenin which are considered high CL systems and (3) the quantum yield for formation of ^{3}NMA* is within experimental error of that expected from intersystem crossing of the chemiexcitation produced ^{1}NMA*.[21] Because of the intrinsically large Φ_f of NMA, potential chemiluminescent systems modeled so as to yield NMA appear highly desirable. Further work along this line is in progress. We also would like to add a note of precaution to others about measuring CL quantum yields from dioxetanes produced *only* by photooxygenation because of the photoinduced decomposition of **2**.

Experimental Section

Materials. Benzene (Mallinckrodt, reagent grade) was distilled through a 20-in. fractionation column and a middle cut was taken. Pyridine (Mallinckrodt, reagent grade) was dried over potassium hydroxide and then fractionally distilled from potassium hydroxide under N_2. Dichloromethane (Mallinckrodt, reagent grade) was purified by filtering through silica gel (Baker, analyzed reagent). Pinacolone (MCB, reagent grade) was fractionally distilled through a 14-in. column and a center cut was collected. Hemin chloride (Calbiochem) and luminol (Aldrich) were used as received.

Synthesis. 10,10′-Dimethyl-9,9′-biacridylidene (1) was prepared by zinc reduction of lucigenin (**3**).[22] The product was purified either by dry-column chromatography on alumina or by recrystallization from pyridine, mp > 360 °C. **1** was assessed pure when a uv–visible absorption spectrum was obtained identical with that reported in the literature.[10]

***N*-Methylacridone (4)** was obtained by N-methylation of acridone using excess methyl iodide in the presence of potassium hydroxide in ethanol–acetone and also from dry-column chromatography of the product of the lucigenin/H_2O_2/HO^- reaction.[5] Acridone was prepared by the method of Allen and McKee.[23]

Zinc Tetraphenylporphine (ZnTP). Into a 300-ml round-bottom flask arranged for magnetic stirring was placed 0.45 g (0.73 mmol) of tetraphenylporphine,[25] 0.32 g (1.46 mmol) of zinc acetate, and 100 ml of dry dimethylformamide. The mixture was refluxed for 1 h. The course of the reaction was monitored by uv–visible absorption spec-

Table I. Thermal Decomposition of Dioxetane 2

Solvent	E_a, kcal mol^{-1}	$\Delta H^{\ddagger}$,[a] kcal mol^{-1}	$\Delta S^{\ddagger}$,[a] eu	K dec (0 °C), s^{-1}
CH_2Cl_2	12.5 (±1.0)	11.9 (±1.0)	−20.3 (±3.7)	0.056 (±0.0006)
CH_2Cl_2 (after column)	17.8 (±0.3)	17.2 (±0.3)	−1.1 (±1.1)	0.056 (±0.006)
Pinacolone	18.7 (±0.3)	18.2 (±0.3)	−1.4 (±1.2)	0.008 (±0.001)
Pyridine	4.0 (±0.6)	3.4 (±0.6)	−55.7 (±2.3)	0.004 (±0.0005)
Pyridine (EDTA)	11.8 (±1.6)	11.3 (±1.6)	−28.5 (±5.9)	0.007 (±0.0005)
Benzene	17.2 (±0.2)	16.7 (±.02)	−5.0 (±2.1)	0.020 (±0.002)

[a] Calculated for 0 °C.

Table II. Light Yields from $^1O_2$ Reaction[a]

Solvent	Φ_{CL}	Φ_f[b]	Φ_{CE}
Pinacolone[c]	6.2×10^{-4}	0.28	2.2×10^{-3}
Pyridine[c]	9.6×10^{-4}	0.34	2.8×10^{-3}
Dichloromethane[c]	7.7×10^{-4}	0.44	1.8×10^{-3}
Dichloromethane[d]	1.60×10^{-2}	0.44	3.61×10^{-2}
Dichloromethane[e]	1.55×10^{-2}	0.44	3.52×10^{-2}

[a] Φ_{CL} = (Einsteins of light)/(moles of NMA produced); $\Phi_{CE} = \Phi_{CL}/\Phi_f$. In a typical run, the NMA yield by fluorometric assay indicated 25–50% consumption of DBA. [b] All under aerated conditions. All measured relative to the quantum yield for NMA fluorescence in aerated ethanol, $\Phi_f = 0.61$, ref 9. [c] Photogeneration of $^1O_2$ using unfiltered light. [d] Photogeneration of $^1O_2$ using CS 3-67 filter. [e] $^1O_2$ via decomposition of triphenyl phosphite ozonide from ozonation of ca. 0.1 M TPP at −78 °C.

troscopy. When the reaction was complete, as judged by the characteristic absorption bands of the product,[26] the mixture was cooled to room temperature and 100 ml of benzene and 50 ml of water were added. The organic layer was separated and the aqueous layer was extracted twice with 100 ml of benzene. The combined benzene layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The product was recrystallized from a 1:1 mixture (v/v) of chloroform/carbon tetrachloride to yield shiny violet plates. The yield was ca. 95%.

Triphenyl phosphite ozonide ($TPPO_3$)[24] was prepared by passing a stream of O_3 (Welsbach ozonator, Model T-408) into a solution of freshly distilled triphenyl phosphite (0.10 M) in dichloromethane at −78 °C until the development of an iodine color in an aqueous KI trap which was placed after the reaction flask. The cold solution was purged with dry N_2 for at least 0.5 h to ensure removal of traces of O_3.

***trans*-Stilbene** (Matheson, scintillation grade, 99.8%) was further purified by preparative gas chromatography using a Hewlett-Packard Model 402B gas chromatograph fitted with a 20% Carbowax on Chromosorb P column at 135 °C. The *trans*-stilbene thus obtained contained <0.02% *cis*-stilbene as determined by flame ionization gas chromatography on the above instrument.

Procedures. Photooxygenations. Aerated samples of DBA (1, ~10^{-4} M) in 7-mm diameter Pyrex tubes were placed in a silvered Dewar equipped with a 2 × 2 in. Pyrex window and irradiated with a Sylvania DWY tungsten iodine lamp (650 W) for ~20 min at −78 °C. When appropriate, as described under Results and Discussion (Table II), a Corning CS-3-67 filter (550-nm short wavelength cutoff) was inserted between the light source and the sample.

Chemiluminescence Spectra. CL spectra were obtained on an American Instrument Co. spectrofluorometer equipped with an IP-21 photomultiplier tube. A clear Pyrex Dewar was put in place of the usual sample holder. The tube containing the photooxygenated solution, or a mixture of DBA and $TPPO_3$, at −78 °C was placed in the Dewar (25 °C) and the CL spectra were immediately recorded during warmup of the samples using a 5-mm slit on the exit of the scanning 0.25-m monochromator (Figure 1). Note that under these low-resolution conditions, the characteristic double peak of NMA fluorescence[10] is not seen.

Kinetic Data. The total CL decay was monitored from photooxygenated samples held at constant temperature in a clear Pyrex Dewar placed immediately in front of the entrance slit to the photomultiplier housing. The samples were introduced into the Dewar in a rigid, reproducible geometry and CL decay curves were obtained over at least 3 half-lives following thermal equilibrium.

Chemiluminescence Quantum Yields. The light yields were measured using the same sample cell configuration as under kinetic data. Photooxygenated or $TPPO_3$–DBA samples were transferred from the −78 °C bath to the sample Dewar (25 °C) and the total light vs. time curves were recorded. Photon yields of emission were determined by comparing the areas under the above CL decays with similar curves obtained from the standardized luminol–hemin–H_2O_2 reaction[17] run in exactly the same geometry. Because of the similarity in the emission spectra from the two systems, no correction for photomultiplier response was needed.

NMA yields were determined by the method of standard additions. The reaction mixture was divided into five equal portions and to each was added a different concentration of a standardized NMA solution. The fluorescence from each solution was recorded. The unknown NMA concentration was determined by plotting fluorescence intensity vs. concentration of added NMA and extrapolating to zero concentration of added NMA. The intercept provides the fluorescence intensity of the unknown NMA and the slope provides the constant relating fluorescence intensity to concentration. Typically, the solutions initially were 1–2 × 10^{-4} M in DBA and the NMA formed was 2–3 × 10^{-4} M indicating 75–100% consumption of DBA.

The quantum yields were calculated from Φ_{CL} = (Einsteins of light)/(moles of NMA produced) and the chemiexcitation quantum yield is given by $\Phi_{CE} = \Phi_{CL}/\Phi_f$. The Φ_f was independently determined under aerated conditions by comparison of the fluorescence from the NMA solutions with that from NMA in aerated ethanol, Φ_f = 0.61.[10]

Note that the CL spectra shown in Figure 1 were run in the presence of 1.0 × 10^{-4} M ZnTP. Under those conditions, a noticeable shift in the NMA fluorescence is observed probably due to reabsorption of the high-energy shoulder by ZnTP which absorbs strongly near 425 nm (422 nm, ϵ 60000).[26] The above light yields were determined in the presence of ~10^{-5} M ZnTP to minimize the reabsorption problem. The similarity of the Φ_{CL} under filtered conditions with the $TPPO_3$ result (Table II) is encouraging on this point.

NMA Triplet Yield. The sensitized *trans* → *cis*-stilbene isomerization reaction[27] was used to measure the yield of ^{3}NMA*. An aerated solution of NMA (1.0 × 10^{-3} M) and *trans*-stilbene (99.8%) (1.0 × 10^{-2} M) was irradiated at 366 nm using a 150-W Xe–Hg arc in conjunction with a 0.25-m American Instrument Co. monochromator. The *cis*-stilbene yield was determined by flame ionization gas chromatography analysis as described above. The photons absorbed were determined by conventional ferrioxalate actinometry. The quantum efficiency for the isomerization was $\Phi_{t\rightarrow c} \sim 1$ after accounting for the singlet to triplet intersystem crossing efficiency of NMA, $\phi_{isc} \sim 0.56$ (from $\phi_{isc} = 1 - \Phi_f$). The apparently very low phosphorescence yield of ^{3}NMA* precluded measuring $^3\Phi_{CE}$ by direct spectroscopic techniques.[28]

The triplet counting experiment was performed by adding the ultrapure *trans*-stilbene (99.98%) (1.0 × 10^{-2} M) to a dichloromethane solution of $TPPO_3$–DBA at −78 °C. The mixture was allowed to warm up to room temperature. The *cis*-stilbene content of this solution (7.7 × 10^{-6} M) was measured by flame ionization gas chromatography under conditions described above. The background *cis*-stilbene was 2 × 10^{-6} M. The NMA yield was determined by fluorescence assay as described above as 1.95 × 10^{-4} M.

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Registry No.—**1**, 23663-77-6; **2**, 59230-86-3; **3**, 2315-97-1; **4**, 719-54-0.

References and Notes

(1) Visiting Associate Professor, University of Southern California, 1974–1975.
(2) E. H. White, J. D. Miano, C. J. Watkins, and E. J. Breaux, *Angew. Chem., Int. Ed. Engl.*, **13**, 229 (1974), and references cited therein.
(3) (a) P. D. Bartlett and A. P. Schaap, *J. Am. Chem. Soc.*, **92**, 3223 (1970); (b) S. Mazur and C. S. Foote, *ibid.*, **92**, 3225 (1970); (c) C. S. Foote, S. Mazur, P. A. Burns, and D. Lerdal, *ibid.*, **95**, 586 (1973); (d) C. S. Foote and J. W. P. Lin, *Tetrahedron Lett.*, 3267 (1968).
(4) F. McCapra and R. A. Hann, *Chem. Commun.*, 442 (1969).
(5) F. McCapra and D. G. Richardson, *Chem. Commun.*, 3167 (1964).
(6) DBA is soluble to the extent of only ca. 2×10^{-4} M in any solvent system. Our measurements were thus limited in several instances by this low solubility.
(7) C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *J. Am. Chem. Soc.*, **90**, 975 (1968).
(8) Under these concentration conditions, >90% of the incident light is absorbed by the sensitizer.
(9) J. R. Totter, V. J. Medina, and J. L. Scoseria, *J. Biol. Chem.*, **235**, 238 (1960).
(10) K. D. Legg and D. M. Hercules, *J. Am. Chem. Soc.*, **91**, 1902 (1969).
(11) (a) T. Wilson, M. E. Landis, A. L. Baumstark, and P. D. Bartlett, *J. Am. Chem. Soc.*, **95**, 4763 (1973); (b) W. H. Richardson and F. C. Montgomery, *ibid.*, **97**, 2819 (1975).
(12) N. J. Turro and P. Lechten, *J. Am. Chem. Soc.*, **95**, 264 (1973).
(13) W. H. Richardson, F. C. Montgomery, M. B. Yelvington, and H. E. O'Neal, *J. Am. Chem. Soc.*, **96**, 7525 (1974).
(14) D. C. S. Lee and T. Wilson in "Chemiluminescence and Bioluminescence", M. J. Cormier, D. M. Hercules, and J. Lee, Ed., Plenum Press, New York, N.Y., 1973, p 265.
(15) C. A. Heller, R. A. Henery, and J. M. Fritsch in ref 14, p 249.
(16) (a) C. S. Foote, A. A. Dzakpasu, and J. W. P. Lin, *Tetrahedron Lett.*, 1247 (1975); (b) H. H. Wasserman and S. Terao, *ibid.*, 1735 (1975).
(17) J. Lee and H. H. Seliger, *Photochem. Photobiol.*, **4**, 1015 (1965).
(18) Light yield is defined as (Einsteins emitted)/(moles of NMA produced).
(19) A control experiment showed that warmup from −78 °C of a dichloromethane solution containing *trans*-stilbene (10^{-2} M) and $TPPO_3$ yielded no detectable increase in *cis*-stilbene over that initially present.
(20) Photolysis at 366 nm of this same reaction mixture yielded additional *cis*-stilbene with near unit quantum efficiency indicating that the products of the DBA–$TPPO_3$ reaction are not inhibitors of the stilbene sensitized isomerization. Hence the ^{3}NMA* counting experiment result is not in need of upward revision.
(21) From the other end of our error limits, we obtain $^1\Phi_{CE} = 0.018$ and Φ of ^{3}NMA* = 0.05 with the *maximum yield of directly formed* NMA* (excluding that from intersystem crossing) being $^3\Phi_{CE} = 0.04$. In view of the relatively large singlet–triplet splitting in NMA (probably $\gtrsim 10$ kcal/mol) we conclude that energetics are not dominating the competition between the chemiexcitation pathways directly leading to singlet and triplet NMA. The extent to which this result depends on the π,π^* nature of the low-lying excited states of NMA needs further elucidation.
(22) H. Decker and W. Petsch, *J. Prakt. Chem.*, **143**, 211 (1935).
(23) C. F. H. Allen and G. H. W. McKee, *Org. Synth.*, **19**, 6 (1939).
(24) R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, **90**, 537 (1968).
(25) G. D. Dorough, J. R. Miller, and F. M. Huennekeus, *J. Am. Chem. Soc.*, **73**, 4315 (1951).
(26) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **85**, 818 (1963).
(27) W. G. Herkstroeter and G. S. Hammond, *J. Am. Chem. Soc.*, **88**, 4769 (1966).
(28) R. N. Nurmukhametov, D. N. Shigonin, L. A. Mileshina, and G. A. Ozerova, *Russ. J. Phys. Chem. (Engl. Transl.)*, **40**, 1186 (1966), report observing phosphorescence from NMA at 77 K in a hexane–dioxane matrix. They place the (0–0) transition at 22 150 cm^{-1} (63.3 kcal/mol) which would suggest a singlet–triplet splitting of ~7–8 kcal/mol. Room temperature phosphorescence has not been reported. It is our view that the 22 150-cm^{-1} emission more likely results from an upper n,π^* triplet with the π,π^* T_1 being closer to 50 kcal/mol.

Transfer Hydrogenation and Transfer Hydrogenolysis. 11. Facile Dehydrogenation of Aromatic Hydrocarbons and the Mechanism of the Hydrogen Transfer from Indan, Tetralin, and Dioxane to Aldehydes Catalyzed by Dihydridotetrakis(triphenylphosphine)ruthenium(II)

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Aromatic hydrocarbons, such as indan and ethylbenzene, were dehydrogenated and reduced aldehydes under mild conditions in the presence of $RuH_2(PPh_3)_4$. It was also found that indan and isobutylbenzene reduced cycloheptene under more drastic condition in the presence of $RhCl(PPh_3)_3$. The mechanism of hydrogen transfer from indan, tetralin, and dioxane to an aldehyde catalyzed by $RuH_2(PPh_3)_4$ was investigated, and found to be different from that of the reduction of aldehydes by alcohols. The transfer hydrogenation by the aprotic substances occurs via dihydride complexes, and the overall rate law was rate $= a[DH_2][cat.]_0/(1 + b[DH_2] + c[RCHO])$ where $[DH_2]$, $[cat.]_0$, and [RCHO] are hydrogen donor, added catalyst, and aldehyde concentrations, respectively. The rate-determining step of the reduction by the aprotic hydrogen donors is the hydrogen transfer from the donors to the catalytic species.

In the catalytic transfer hydrogenation of carbonyl compounds, only primary and secondary alcohols[1] and formic acid[2] have been reported to donate hydrogen atoms under rather drastic conditions. We previously reported that ethers and hydroaromatic compounds also reduced aldehydes and ketones, and discussed the mechanism of the hydrogen transfer from alcohols to aldehydes catalyzed by $RuH_2(PPh_3)_4$.[3] Later, we found that aromatic hydrocarbons also gave hydrogen to aldehydes under mild conditions and to olefins under more drastic conditions. This study was undertaken to investigate the difference between the mechanism of the transfer hydrogenation of aldehydes by the protic hydrogen donors, alcohols, and that of the one by aprotic donors such as indan, tetralin, and dioxane.

Results and Discussion

Hydrogen-Donating Ability of Aromatic Hydrocarbons. Although the dehydrogenation of aromatic hydrocarbons has been carried out under drastic conditions in the presence of heterogeneous catalysts, we found that the dehydrogenation occurred under mild conditions with homogeneous catalysts. When an aromatic hydrocarbon (2.0 M), *n*-hexaldehyde (1.0 M), and $RuH_2(PPh_3)_4$ (0.02 M) were heated in bromobenzene at 36.5 °C, *n*-hexyl alcohol and a

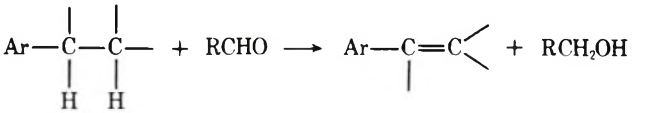


Table I. Transfer Hydrogenation of *n*-Hexaldehyde and Cycloheptene

Registry no.	Hydrogen donor	Yield of *n*-hexyl alcohol, % I[a]	II[b]	Dehydrogenation product
25340-17-4	Diethylbenzene	12	24	[c]
496-11-7	Indan	13	22	Indene
25340-18-5	Triethylbenzene	11	21	[c]
104-51-8	*n*-Butylbenzene	10	20	[c]
538-93-2	Isobutylbenzene	10	20	1-Phenyl-2-methylpropene-1
1515-95-3	*p*-Ethylanisole	10	20	[c]
100-41-4	Ethylbenzene	9	18	Styrene
103-65-1	*n*-Propylbenzene	10	18	1-Phenylpropene-1
98-82-8	Isopropylbenzene	9	16	α-Methylstyrene
100-71-0	2-Ethylpyridine	11	15	[c]
6623-59-2	3,4-Dichloroethylbenzene	7	9	[c]
	Indan		28[d]	Indene
	Isobutylbenzene		9[d]	1-Phenyl-2-methylpropene-1

[a] $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde (1.0 M), and the hydrogen donor (2.0 M) were heated in bromobenzene at 36.5 ± 0.5 °C for 72 h. [b] $RuH_2(PPh_3)_4$ (0.02 M) and *n*-hexaldehyde (1.0 M) were heated in the designated hydrogen donor at 120 °C for 4 h. [c] Dehydrogenation product was not identified. [d] $RhCl(PPh_3)_3$ (0.02 M) and cycloheptene (0.5 M) were heated in the designated hydrogen donor at 180 °C for 6 h.

Table II. Transfer Hydrogenation of Carbonyl Compounds[a]

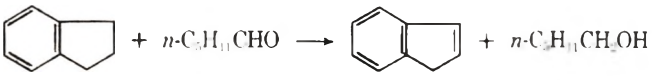
Registry no.	Substrate	Product	% yield
66-25-1	*n*-Hexaldehyde	*n*-Hexyl alcohol	22
110-62-3	*n*-Pentaldehyde	*n*-Pentyl alcohol	20
123-72-8	*n*-Butylaldehyde	*n*-Butyl alcohol	20
111-71-7	*n*-Heptaldehyde	*n*-Heptyl alcohol	16
123-38-6	Propionaldehyde	*n*-Propyl alcohol	16
124-13-0	*n*-Octaldehyde	*n*-Octyl alcohol	15
123-05-7	2-Ethyl-1-hexaldehyde	2-Ethyl-1-hexyl alcohol	14
78-93-3	Methyl ethyl ketone	2-Butyl alcohol	7
96-22-0	Diethyl ketone	3-Pentyl alcohol	7
67-64-1	Acetone	Isopropyl alcohol	6
100-52-7	Benzaldehyde	Benzyl alcohol	Trace

[a] $RuH_2(PPh_3)_4$ (0.02 M) and the substrate (1.0 M) were heated in indan at 120 °C for 4 h.

dehydrogenation product were obtained. However, the hydrogen transfer reaction was not catalyzed by $RhH(PPh_3)_4$, $RuCl_2(PPh_3)_3$, and $RhCl(PPh_3)_3$ even at 120 °C. As shown in Table I, all the aromatic hydrocarbons showed almost the same hydrogen-donating ability, and the yield of *n*-hexyl alcohol was quite low. This reaction is thought to be equilibrium limited, because the yield of *n*-hexyl alcohol was not improved by prolonged heating. This phenomenon is interpreted by the explanation that the alcohol produced is easily dehydrogenated to give the original aldehyde because the hydrogen-donating ability of the alcohol is superior to that of the aromatic hydrocarbons.

$$R^1CHO + R^2CH_2OH \rightarrow R^1CH_2OH + R^2CHO$$

When the reaction was carried out in the hydrogen donor at 120 °C, the yield of the alcohol somewhat increased. In substituted ethylbenzenes, the hydrogen-donating ability decreased in the order 4-ethylanisole > ethylbenzene > 3,4-dichloroethylbenzene. The hydrogen-donating ability is lowered by the electron-withdrawing substituents and this suggests the formation of cationic species in the transition state of the rate-determining step. Dehydrogenated donors were not quantitatively obtained except for indan. The complex $RuH_2(PPh_3)_4$ has been reported to catalyze the polymerization of olefinic compounds,[4] so the dehydrogenated alkylbenzenes are inferred to be lost by the polymerization. In the case of indan, the amount of the alcohol produced was equal to that of indene within experimental errors, and the following reaction is considered to proceed without significant side reactions.



The hydrogen transfer from indan and isobutylbenzene to cycloheptene also took place in the presence of $RhCl(PPh_3)_3$, but the reduction was hardly catalyzed by $RuH_2(PPh_3)_4$ and $RuCl_2(PPh_3)_3$.

Transfer Hydrogenation of Carbonyl Compounds. The reduction of several carbonyl compounds was examined in indan at 120 °C (Table II), and aliphatic aldehydes were found to be reduced most easily. The yield of the alcohols was not varied so much with the structure of the aliphatic aldehydes, but the aldehydes having moderate steric hindrance were inclined to give the corresponding alcohols in higher yield. The steric effect is explained by these assumptions: (1) As shown later (Scheme II), the coordination of two aldehyde molecules may inhibit the transfer hydrogenation, and the most appropriate coordinating power of the aldehydes exists. (2) As described earlier, this reaction is equilibrium limited, and the alcohol formed competes with the other hydrogen donor for a coordination site of the catalyst. Therefore, in the balance of the coordinating power between the aldehydes and the corresponding alcohols which is affected by the alkyl residues of the aldehydes, the most favorable steric hindrance of the aldehyde exists. Aliphatic ketones were more difficultly re-

Table III. Solvent Effect [a]

Solvent	Rate, mol $l.^{-1}$ min^{-1} × 10^3	Solvent	Rate, mol $l.^{-1}$ min^{-1} × 10^3
Benzene	1.8	Chlorobenzene	1.4
p-Xylene	1.8	Diethyl ether	1.4
o-Dichlorobenzene	1.8	Methyl benzoate	1.3
n-Hexane	1.7	Acetonitrile	1.1
Bromobenzene	1.4	Dimethyl sulfoxide	1.1
Anisole	1.4		

[a] $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde (1.0 M), and indan (2.0 M) were heated at 80 °C.

duced, perhaps because the secondary alcohols formed are more effective as hydrogen donors than the primary alcohols. Benzaldehyde and acetophenone were hardly reduced, and this fact is interpreted by the explanation that the carbonyl group is stabilized by the resonance with the benzene ring and the hydrogen donating ability of benzylic alcohols is stronger than that of the other aliphatic alcohols. *N,N*-Dimethylacetamide and ethyl acetate were not reduced.

Unless otherwise noted, *n*-hexaldehyde was used as a hydrogen acceptor in all the experiments in this study, because of the ease in GC analysis.

Reaction Solvent. Although the transfer hydrogenation of olefins hardly proceeded in polar solvent such as chlorobenzene,[5,6] the rate of the reduction of *n*-hexaldehyde by indan was not influenced so much by solvents (Table III). This observation shows that the coordination of the aldehyde is stronger than that of olefins and so strong as not to be affected by solvents. The strong coordination ability of aldehydes has been shown by spectroscopic study[3] and by the effect of addition of triphenylphosphine and olefins. In spite of the low solubility of the catalyst in *n*-hexane and ether at room temperature, it immediately dissolved to give a red-brown solution in the presence of the aldehyde. This also shows that the aldehyde coordinates so strongly as to form a complex rapidly with the catalyst. In the other experiments in this study, bromobenzene was used as a solvent.

Measurement of Initial Rate. We have previously reported that the hydrogen transfer from tetralin and dioxane to *n*-hexaldehyde catalyzed by $RuH_2(PPh_3)_4$ occurred without side reactions.[3] Then the kinetic study of the reduction of the aldehyde, in which indan, tetralin, and dioxane were used, was carried out to investigate the reaction mechanism and to compare it with the mechanism of the reduction by alcohols. The yield of the alcohol was proportional to the reaction time up to several percent as shown in Figure 1 and the initial rate of the reduction (R) was derived from the linear part. The linear part was narrower than that of other transfer hydrogenations and it is inferred to be caused by the dehydrogenation of the produced alcohol.

The initial rate of the reduction was proportional to the catalyst concentration (Figure 2), and the plot of the reciprocal of the rate against the reciprocal of the concentration of the hydrogen donors was linear with a positive intercept on the y axis (Figure 3). In the reduction of the aldehyde by alcohols, the rate was in proportion to the concentration of the alcohol.[3] The difference in the dependence of the rate on the hydrogen donor concentration may be due to the difference in the reaction mechanisms. The initial rate of the reduction decreased with the increase of the aldehyde concentration. The plot of the reciprocal of the rate against the aldehyde concentration was linear with a positive intercept on the y axis, as shown in Figure 4. This agrees with the result obtained in the reduction by alcohols.[3]

Reaction Temperature. Initial rates were measured at several temperatures ranging from 60 to 110 °C, and the plots of log R against $1/T$ show a good linear relationship. From the

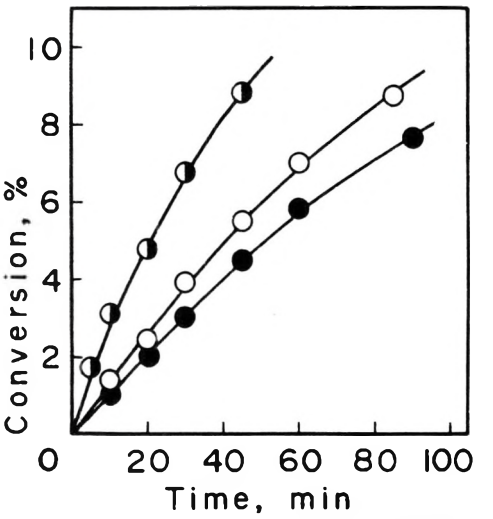


Figure 1. Plots of conversion vs. reaction time: $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde (1.0 M), and the hydrogen donor were heated in bromobenzene at 80 °C; (○) indan, (●) dioxane (2.0 M), and (◑) tetralin (1.0 M).

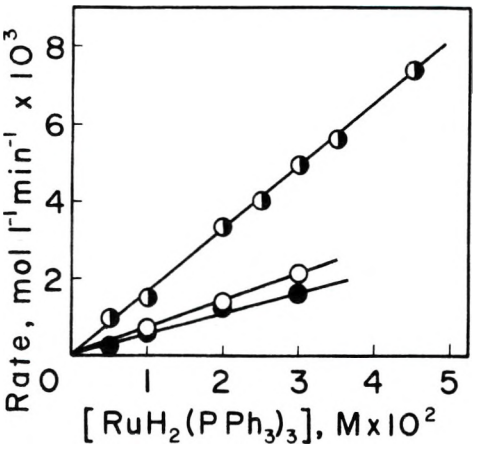


Figure 2. Dependence of the rate of the reduction of *n*-hexaldehyde on catalyst concentration: the catalyst, *n*-hexaldehyde (1.0 M), and the hydrogen donor were heated in bromobenzene at 80 °C; (○) indan, (●) dioxane (2.0 M), and (◑) tetralin (1.0 M).

plots, activation energy, E_a, and activation enthalpy, $\Delta H^{\ddagger}$, were obtained, and activation entropy, $\Delta S^{\ddagger}$, was derived from the rate constant, k_4, which will be defined later. The values of the corresponding parameters were nearly equal mutually in the reduction of the aldehyde by indan, dioxane, and tetralin (Table IV). This suggests the similarity in the reaction mechanism. The activation energy and the activation enthalpy of the reduction by isopropyl alcohol are higher than those of the corresponding reduction by the aprotic hydrogen donors. Further, the values of the three parameters of the reductions of the aldehyde by the protic and the aprotic hydrogen donors are greatly lower than those of the corresponding parameters

Table IV. Kinetic Parameters

Registry no.	Hydrogen donor	Hydrogen acceptor	E_a, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
	Indan	*n*-Hexaldehyde	7.4	6.7	−44.3
119-64-2	Tetralin	*n*-Hexaldehyde	6.8	6.1	−43.3
123-91-1	Dioxane	*n*-Hexaldehyde	6.8	6.1	−46.3
67-63-0	Isopropyl alcohol	*n*-Hexaldehyde	11.0	10.3	−42.5
	Isopropyl alcohol	Cyclohexene	31.4	30.7	20

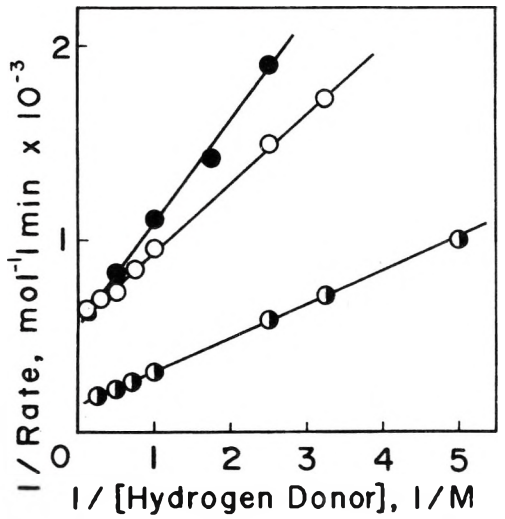


Figure 3. Dependence of the rate of the reduction of *n*-hexaldehyde on the hydrogen donor concentration: $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde (1.0 M), and the hydrogen donor were heated in bromobenzene at 80 °C; (○) indan, (●) dioxane, and (◑) tetralin.

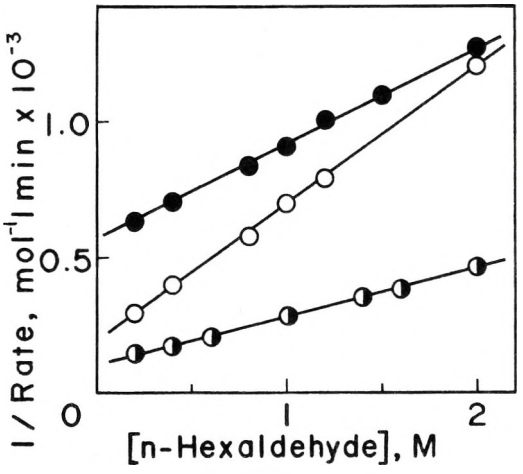


Figure 4. Dependence of the rate of the reduction of *n*-hexaldehyde on the aldehyde concentration: $RuH_2(PPh_3)_4$ (0.02 M), *n*-hexaldehyde, and the hydrogen donor were heated in bromobenzene at 80 °C; (○) indan, (●) dioxane (2.0 M), and (◑) tetralin (1.0 M).

of the reduction of cyclohexene by the alcohol. The small value of the activation entropy indicates that the transition states of the reductions of the aldehydes are more crowded or more ordered than that of the hydrogenation of olefins.[7] Therefore, the reaction mechanism for the reduction of aldehydes by the protic and the aprotic compound considerably differed from that of olefins by alcohols.

Kinetic Isotope Effect. The initial rate was 1.1×10^{-3} mol l.$^{-1}$ min^{-1} in the reaction in which *n*-hexaldehyde (1.0 M), dioxane (1.0 M), and the catalyst (0.2 M) were heated in bromobenzene at 80 °C, while it was 5.5×10^{-4} mol l.$^{-1}$ min^{-1} in the reduction in which octadeuteriodioxane was used instead of dioxane. The value of the kinetic isotope effect, R_H/R_D = 2.0, shows that a hydrogen transfer step is rate limiting. In this reaction, the hydrogen transfer occurs twice. One is the transfer from the hydrogen donor to the central metal of the catalyst and the other is that from the dihydride complex to the coordinated aldehyde. The former is inferred to be rate limiting, because the reaction between *n*-hexaldehyde and $RuH_2(PPh_3)_4$ completed within 1 min at 80 °C and quantitatively gave *n*-hexyl alcohol as a product. Unlike this result, the value of the kinetic isotope effect was 0.9 in the reduction of the aldehyde by isopropyl alcohol, and the coordination of the alcohol is concluded to be the rate-determining step.[3] Based on the fast hydrogen transfer from $RuH_2(PPh_3)_4$ to the aldehyde, the first step of the catalytic cycle is considered to be the transfer of the hydride ligands of the complex to aldehyde, as reported previously.[3,6]

Scheme I

$$RuH_2(PPh_3)_4 + RCHO \rightarrow RuH_2(PPh_3)_3(RCHO) + PPh_3$$

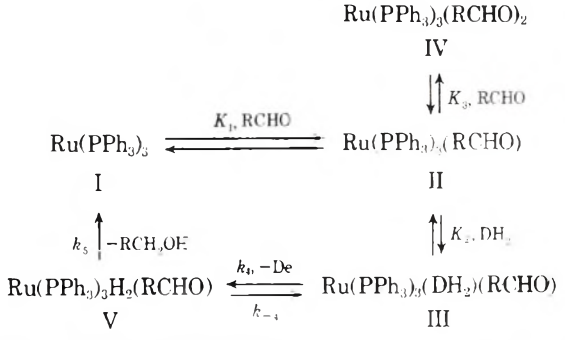
$$RuH_2(PPh_3)_3(RCHO) \xrightarrow{S} Ru(PPh_3)_3 + RCH_2OH$$

S = solvent

Effect of Additives. To investigate the reaction process, the effect of additives was examined at 80 °C. Although the rate of the transfer hydrogenations of olefins was lowered by the addition of triphenylphosphine in almost all cases,[5,6,8] that of the reduction of the aldehydes by the aprotic hydrogen donors was not changed at all by the addition of the phosphine over concentration range of 0.01–0.1 M. This fact shows that the release of the phosphine from the catalyst occurs easily. The rate of the reduction of the aldehyde was not decreased by the addition of indene, dioxene, cyclohexene, and hexene-1, and neither the hydrogenation of cyclohexene and hexene-1 nor the isomerization of hexene-1 was observed. This fact suggests that the coordinating ability of the aldehyde is far larger than that of the olefins and the dehydrogenated donors, and perhaps larger than that of hydrogen donors which seems to be comparable to that of the dehydrogenated donors. The addition of ethyl alcohol increased the rate of the reduction of the aldehyde, because the alcohol acts as a hydrogen donor. This observation is consistent with the early deviation from the linear dependence of the conversion of the aldehyde against reaction time, as described before.

Kinetic Discussion. The studies of the hydrogen transfer from isopropyl alcohol to olefins[6] and aldehydes[3] by $RuH_2(PPh_3)_4$ have been already reported. Based on those studies and the results described in the previous section, we should like to propose the following catalytic cycle for the

Scheme II



DH_2 = hydrogen donor, De = dehydrogenated donor

reaction scheme of the reduction of the aldehyde by the aprotic hydrogen donors. The first step of this transfer hydrogenation is presumed to be the formation of $Ru(PPh_3)_3$ or its solvated species, as described earlier.

It is assumed that the intermediate, V, is sufficiently reactive and scarce for steady-state treatment to be applied, because the reaction between $RuH_2(PPh_3)_4$ and *n*-hexaldehyde occurred very fast. From the assumption and Scheme II, the rate is expressed as

$$R = \frac{k_4k_5K_1K_2[\mathrm{RCHO}][\mathrm{DH_2}][\mathrm{cat.}]_0}{(k_{-4}[\mathrm{De}] + k_5)[1 + K_1[\mathrm{RCHO}](1 + K_3[\mathrm{RCHO}] + K_2[\mathrm{DH_2}])]} \quad (1)$$

where K_1, K_2 and K_3 are equilibrium constants, k_4 and k_5 are rate constants, and $[DH_2]$, [RCHO], [De], and $[cat.]_0$ are the concentration of the hydrogen donors, the aldehyde, the dehydrogenated donors, and the added catalyst, respectively. As the dehydrogenated donors were not reduced, the term of $k_{-4}[De]$ is negligible. Then eq 1 is reduced to

$$R = \frac{k_4K_1K_2[\mathrm{RCHO}][\mathrm{DH_2}][\mathrm{cat.}]_0}{1 + K_1[\mathrm{RCHO}](1 + K_3[\mathrm{RCHO}] + K_2[\mathrm{DH_2}])} \quad (2)$$

As the reciprocal of the rate depended linearly on the aldehyde concentration, the following relation should be satisfied in the denominator of eq 2: $1 \ll K_1[RCHO](1 + K_3[RCHO] + K_2[DH_2])$, that is, I ≪ II + III + IV. This relation is consistent with the fact that the coordination power of the aldehyde is strong. Therefore, eq 3 becomes

$$R = \frac{k_4K_2[\mathrm{DH_2}]}{1 + K_2[\mathrm{DH_2}] + K_3[\mathrm{RCHO}]}[\mathrm{cat.}]_0 \quad (3)$$

This expression accommodates all the experimental results. As an example of the analysis of eq 3, the reduction by dioxane is described. (a) The rate shows the first-order dependence on the catalyst concentration in both Figure 1 and eq 3, and the value of 0.028 min^{-1} was obtained as the value of the coefficient of the catalyst concentration in eq 3 from the gradient of the plot of Figure 1. (b) Equation 3 is rearranged as follows:

$$1/R = \frac{1}{k_4[\mathrm{cat.}]_0} + \frac{1 + K_3[\mathrm{RCHO}]}{k_4K_2[\mathrm{cat.}]_0}\frac{1}{[\mathrm{DH_2}]} \quad (4)$$

This equation is consistent with the plot of Figure 2, and the value of the intercept, 580 mol^{-1} l. min, and the one for the gradient, 600 min, were obtained as the value of the first term and the coefficient of the second term, respectively. (c) Equation 3 can be rearranged as follows:

$$1/R = \frac{1 + K_2[\mathrm{DH_2}]}{k_4K_2[\mathrm{DH_2}][\mathrm{cat.}]_0} + \frac{K_3}{k_4K_2[\mathrm{DH_2}][\mathrm{cat.}]_0}[\mathrm{RCHO}] \quad (5)$$

From Figure 3, the value for the intercept, 600 $mol\ l.^{-1}$ min, and the one for the gradient, 280 $mol^{-2}\ l.^2$ min, were obtained as the value of the first term and the coefficient of the second term of eq 5, respectively. From these values, 6.3 mol^{-1} l., 6.4 mol^{-1} l., and 0.09 min^{-1} were obtained as the values of K_2, K_3, and k_4. Therefore, in the reduction of *n*-hexaldehyde by dioxane in bromobenzene at 80 °C, the overall rate is expressed as follows:

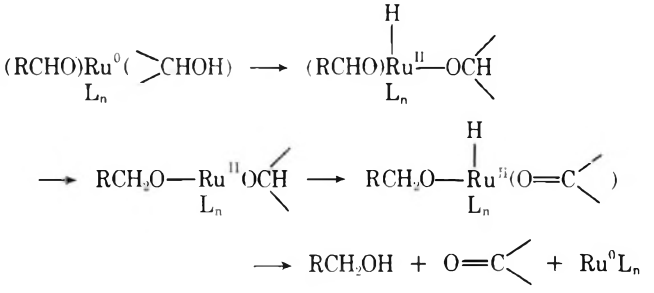
$$R = \frac{0.57[\mathrm{DH_2}][\mathrm{cat.}]_0}{1 + 6.3[\mathrm{DH_2}] + 6.4[\mathrm{RCHO}]} \quad (6)$$

The values of K_2, K_3, and k_4 are summarized in Table V. The relative values of the coordinating power of the hydrogen donors may be estimated by the values of K_2/K_3 ratio, and that of dioxane was found to be a little larger than that of indan and tetralin. This may be due to the difference of the way of the coordination, that is, dioxane coordinates on the catalyst with the oxygen, while indan and tetralin do with their benzene rings. The value of k_4 in the reaction of tetralin was about four times larger than that in the reaction of indan or dioxane. This fact might be explained by the relative stability of the intermediates derived from the donors.[9] The similarity of all the kinetic behaviors and constants except for k_4 indicates that the hydrogen transfer from indan, tetralin, and dioxane to aldehydes occurs in a similar way. However, the mechanism of this reduction is different from that of the reduction of aldehydes by alcohols. As described before, the outcome of the kinetic isotope effect varied one from another. Moreover, the rate was proportional to the donor concentration in the reduction by alcohols, but such a relation was not observed in the reduction by the aprotic hydrogen donors. According to the hydrogen transfer from alcohols to aldehydes, we previously proposed such a mechanism as shown in Scheme III, which involves the oxidative addition of O–H bond to a Ru^0 species.[3] The coordination of alcohols is concluded to be the rate-determining step.

Table V. Kinetic and Equilibrium Constants

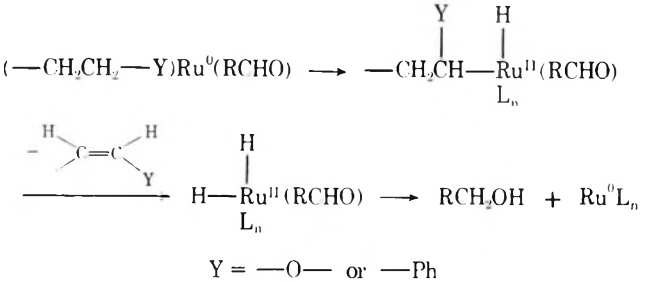
Hydrogen donor	k_4, min^{-1}	K_2, mol $l.^{-1}$	K_3, mol $l.^{-1}$	K_2/K_3
Indan	0.11	5.0	5.5	0.91
Tetralin	0.42	3.8	4.2	0.90
Dioxane	0.09	6.3	6.4	0.98

Scheme III



This mechanism cannot be applied to the reduction by the aprotic donors. Therefore, we should like to propose the following mechanism in which the oxidative addition of a C–H bond is the rate-determining step.

Scheme IV



Y = —O— or —Ph

The mechanism of the reduction of aldehydes by the protic and aprotic hydrogen donors is different from that of the reduction of olefins by alcohols. This is supported by the fact that aldehydes coordinated rapidly on ruthenium species but olefins hardly did, and that in the reduction of olefins by alcohols ruthenium species exist mainly in the form of $Ru(PPh_3)_3$ or its solvated form,[6] while in the reduction of aldehydes by alcohols a ruthenium–aldehyde complex was obtained.[3] The transfer hydrogenation of aldehydes occurred at lower temperatures than that of olefins.[3] This fact suggests that the catalyst was activated by the coordination of one aldehyde molecule, because the dehydrogenation from the donors is rate limiting both in the reduction of olefins by alcohols

and in that of aldehydes by the aprotic donors. Anyway, the relative strength of the coordinating power of hydrogen donors and hydrogen acceptors is one of the important factors to control the reaction mechanisms of transfer hydrogenations.

In the reduction at 80 °C in bromobenzene, tetralin, 1,2-dihydronaphthalene, and 1,4-dihydronaphthalene reduced *n*-hexaldehyde at the initial rate of 3.2, 8.5, and 2.5×10^{-3} mol $l.^{-1}$ min^{-1}, respectively. 1,4-Dihydronaphthalene showed the lowest reduction rate, and the rate of the isomerization to 1,2-dihydronaphthalene was far higher than that of the reduction of the aldehyde. We formerly considered that the driving force of the hydrogen transfer from tetralin was the increase of the aromatization energy caused by the formation of naphthalene. However, the dehydrogenation rate of dihydronaphthalenes was not so much higher than that of tetralin. Moreover, it was found that the main product in the earlier stage of the reduction of aldehydes by tetralin was not naphthalene but 1,2-dihydronaphthalene. These results show that the driving force of the hydrogen-donating ability of tetralin was not derived from the stabilization by the aromatization. We now consider that the hydrogen donating abilities of the aprotic donors examined were affected by the stabilities of the cationic intermediates.

Experimental Section

All the transfer hydrogenations and kinetic measurements were carried out by the method reported previously.[3,5,6,8,10]

Materials. Chlorotris(triphenylphosphine)rhodium(I),[12] dichlorotris(triphenylphosphine)ruthenium(II),[13] hydridotetrakis(triphenylphosphine)rhodium(I),[14] and dihydridotetrakis(triphenylphosphine)ruthenium(II)[14] were prepared by methods reported in the literature. Aldehydes were purified by distillation followed by dehydration with molecular sieves. Tetralin, indan, 1,2-dihydronaphthalene, and dioxane were purified by distillation and dried by usual methods. All solvents were purified by distillation. 1,4-Dihydronaphthalene and 3,4-dichloroethylbenzene were synthesized by methods of Cook[15] and Marvel,[16] respectively.

Registry No.—Cycloheptene, 628-92-2; hexyl alcohol, 111-27-3; dihydridotetrakis(triphenylphosphine)ruthenium(II), 19529-00-1.

References and Notes

(1) (a) J. C. Orr, M. Mersereau, and A. Sanford, *Chem. Commun.*, 162 (1962); (b) Y. M. Y. Haddad, H. B. Henbest, J. Husbands, and T. R. B. Mitchell, *Proc. Chem. Soc., London*, 361 (1964); (c) E. L. Eliel, T. W. Doyle, R. O. Hutchins, and E. C. Gilbert, *Org. Synth.*, **50**, 13 (1970); (d) M. Gullotti, R. Ugo, and S. Collonna, *J. Chem. Soc. C*, 2652 (1971); (e) Y. M. Y. Haddad, H. B. Henbest, J. Husbands, T. R. B. Mitchell, and J. Trocha-Grimshaw, *J. Chem. Soc., Perkin Trans. 1*, 596 (1974); (f) E. Malunowicz and S. Tyrlik, *J. Organomet. Chem.*, **72**, 269 (1974); (g) Y. Sasson, P. Albin, and J. Blum, *Tetrahedron Lett.*, 833 (1974); (h) J. Blum and Y. Sasson, *J. Org. Chem.*, **40**, 1887 (1975).

(2) R. S. Coffey, *Chem. Commun.*, 923 (1967).

(3) H. Imai, T. Nishiguchi, and K. Fukuzumi, *J. Org. Chem.*, **41**, 665 (1976).

(4) S. Komiya, A. Yamamoto, and S. Ikeda, *Bull. Chem. Soc. Jpn.*, **48**, 101 (1975).

(5) H. Imai, T. Nishiguchi, and K. Fukuzumi, *J. Org. Chem.*, **39**, 1622 (1974).

(6) H. Imai, T. Nishiguchi, M. Kobayashi, and K. Fukuzumi, *Bull. Chem. Soc. Jpn.*, **48**, 1585 (1975).

(7) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1959, p 181.

(8) T. Nishiguchi, K. Tachi, and K. Fukuzumi, *J. Org. Chem.*, **40**, 237, 240 (1975).

(9) The hydrogen donor seems to be cationic in the transition state of the dehydrogenation catalyzed by transition metal complexes.[1b,10,11] This inference is supported by the substituent effect of ethylbenzenes which was described earlier. The cationic intermediate derived from tetralin seems to have higher stability than the one from indan. This reasoning is based on the inference that the nine carbon atoms of them have a tendency to lie in a plane by the benzyl type resonance (this means that all the carbon atoms of the intermediate derived from indan endeavor to lie in a plane).

(10) T. Nishiguchi and K. Fukuzumi, *J. Am. Chem. Soc.*, **96**, 1893 (1974).

(11) G. N. Schrauzer, "Transition Metals in Homogeneous Catalysis", Marcel Dekker, New York, N.Y., 1971, p 108.

(12) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).

(13) T. A. Stephenson and G. Wilkinson, *J. Chem. Soc. A*, 2660 (1968).

(14) J. J. Levison and S. D. Robinson, *J. Chem. Soc. A*, 2947 (1970).

(15) E. S. Cook and A. J. Hill, *J. Am. Chem. Soc.*, **62**, 1996 (1940).

(16) C. S. Marvel, C. G. Overberger, R. E. Allen, H. W. Johnston, J. H. Saunders, and J. D. Young, *J. Am. Chem. Soc.*, **68**, 861 (1946).

A Survey of Structural Effects on Formation Constants in C–H Hydrogen Bonding[1]

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Formation constants, K, for the association of a variety of C–H donors with HMPA have been measured by application of Higuchi's iterative method to ^1H NMR data for CCl_4 solutions at 35 °C. Infrared shifts have been measured using Me_2SO-d_6 in CCl_4 or $CDCl_3$. The donors include sp^3, sp^2, and sp systems. As previously reported, K's correlate so poorly with ir shifts that the latter have no predictive value as to the strength of H-bond complex formation for C–H donors. The largest K's are found in sp^3 systems because of the possibility of three electronegative α substituents. K's for terminal acetylenes are more sensitive to their single β substituent, covering a range of at least 100-fold. K's are reported for the first time for vinyl and aromatic C–H bonds; those for the latter are small. Substituents affect K values for sp^3 systems in the order $CN \simeq NO_2 > SCN$, p-O_2N-$C_6H_4 > F, Cl, Br > CONMe_2 > CO_2R \geq C_6H_5$, which differs markedly from that observed for Bronsted proton transfer in solution. Similar orders are followed in the sp^2 and sp series. Substituent effects are only crudely correlated by Taft σ_I constants. It is suggested that substituent effects in C–H hydrogen bonding reflect a greater contribution from the through-bond inductive effect than in other systems.

The participation of C–H bonds in hydrogen bonding has long been recognized, as for chloroform and terminal acetylenes.[2] Their hydrogen bonds with strong acceptors, such as pyridine and Me_2SO, as well as with weaker ones such as acetone, are readily detected by ir and ^1H NMR spectral shifts. A detailed survey of ir shifts by Allerhand and Schleyer,[3] utilizing fully deuterated Me_2SO and pyridine, has shown clearly that certain vinyl and aromatic C–H bonds also undergo hydrogen bonding, and that shifts for saturated systems are enhanced much more by an α-cyano group than by α-

chlorine or α-bromine. Some studies by ^{1}H NMR have been carried out, but these were restricted to haloforms and related polyhalides[4] and phenylacetylene.[5] Formation constants have been reported for very few donors.

The available data raise questions about the extent of hydrogen bonding by C–H bonds which can only be answered with formation constants. How is hydrogen bonding ability affected by hybridization at carbon? Is there any correlation between ir shifts and formation constants? Does an increase in the ir shift due to an α-cyano group in fact signal an increase in the formation constant, and if so, do any other substituents, especially nitro, rival cyano in their effect on C–H hydrogen bonding ability? What is the order of substituent effects, and what factors determine this order?

We have previously reported[6] formation constants for several donors with the strong acceptor hexamethylphosphoramide (HMPA) in CCl_4 at 35 °C. We found the constants, or K's, to fall in the order $Br_2CHCN \sim F_2CHCN > HCCl_3 > Cl_2C{=}CHCl \sim C_6H_5C{\equiv}CH$ and to fail completely to correlate with ir shifts, $-\Delta\bar{\nu}$.

We shall here present more precise formation constants for a greater variety of donors, and discuss the effects of substituents and hybridization on these.

Results

Infrared Shifts. Infrared shifts, $-\Delta\bar{\nu}$, have been measured for a few compounds using 1.0 M Me_2SO-d_6 in CCl_4 or $CDCl_3$ in well matched 0.5 or 1.0 mm sodium chloride cells. The values, in cm^{-1}, are reported in Tables I and II along with those previously measured.[6] Me_2SO-d_6 has been used for the sake of continuity with the work of Allerhand and Schleyer,[3] because the preparation of HMPA-d_{18} would probably be costly out of proportion to its usefulness, and because the few K's which we have measured by ^{1}H NMR using Me_2SO are reasonably proportional to K's for HMPA. Deuterium labeled acceptors are necessary in ir work to prevent the C–H stretching region from being rendered opaque by the more concentrated acceptor.

Measurement of Formation Constants. Two modifications have been introduced into our procedure for measuring hydrogen bond formation constants. The first, allowing a great improvement in the precision of δ, is the use of internal lock combined with sidebanding and frequency counting equipment. These features were absent from the spectrometer previously available to us.

The second modification is the Higuchi iterative method[7] of calculating K, involving eq 1, which is derived without any simplifying approximations for 1:1 complexing only. The advantages of the Higuchi method are that it is convergent, it is readily adaptable to digital computer programming, and it permits the easy identification of divergent data points.

$$\frac{C_b}{\delta_{obsd} - \delta_a} = \frac{C_a + C_b - C_c}{\delta_c - \delta_a} + \frac{1}{K(\delta_c - \delta_a)} \quad (1)$$

In eq 1, C_a and C_b are total concentrations of acid (donor) and base (acceptor), respectively, and C_c that of 1:1 complex, δ_{obsd} is the chemical shift of donor in the presence of acceptor at concentration C_b, δ_a the shift of donor in the absence of acceptor, δ_c the (usually hypothetical) shift of the complexed proton, and K the formation constant.

Equation 1 is applied by plotting the left side vs. $(C_a + C_b)$; the slope is used as an approximation to $1/(\delta_c - \delta_a)$ for calculation of trial values of C_c via eq 2, and a second plot, using $(C_a + C_b - C_c)$, is constructed, giving an improved value of $1/(\delta_c - \delta_a)$.

$$C_c = C_a \frac{\delta_{obsd} - \delta_a}{\delta_c - \delta_a} \quad (2)$$

This cycle of calculations and plots is repeated until the slope remains constant within desired limits. The final plot is examined, deviant points rejected, the iterative procedure repeated, and finally $(\delta_c - \delta_a)$ and K calculated (from eq 1, K = slope/intercept).

In the present study, the Higuchi method has given plots of excellent linearity in most cases for which $K \geq 1.0$ M^{-1}, and acceptable plots for $0.2 \leq K \leq 1.0$. In some cases, e.g., phenyldinitromethane, the Higuchi method succeeded where the previous method[1,6] had failed,[1] viz., calculating K for a wide range of trial values of $(\delta_c - \delta_a)$ and choosing that value for which the K's had the smallest percent standard deviation. In other cases it gave results in good agreement with those of the other method. The Higuchi method failed only for very weak donors giving small shifts, e.g., *tert*-butylacetylene and 1,3,5-trichlorobenzene, and, as indicated above, where K was much less than 0.2 M^{-1}.

Attempts to determine K's much smaller than 0.2 M^{-1} by using higher HMPA concentrations than 1.5 M usually led to curvature of Higuchi plots. This is a reasonable consequence of the effect on chemical shift of changing bulk diamagnetic anisotropy. In the case of *tert*-butylacetylene, this effect was so marked that the Higuchi plot actually had a negative slope. Although good plots were obtained for phenylacetylene in both CCl_4 and cyclohexane, $\delta_c - \delta_a$ was twice as great in CCl_4 (4.0 vs. 2.0 ppm in cyclohexane). For donors with larger K's, $\delta_c - \delta_a$ values were more nearly the same in the two solvents. The results for phenylacetylene in CCl_4 are therefore also rendered unreliable because of the bulk anisotropy effect.

The principal limitation of the Higuchi method is its restriction to 1:1 complexing. It is desirable to overcome this limitation, since certain compounds with two or more protons are of considerable interest, e.g., malononitrile and fumaronitrile, typical of disubstituted methanes and ethylenes. We believe that we have approached success in these two cases, by the simple expedient of repeating the measurements at the lowest concentrations consistent with observation of the proton resonance, thus minimizing the concentration of 2:1 complex. Indeed, the plots were linear, although they had been concave down at higher concentrations, $C_a \sim 0.1$ M and $0.1 < C_b < 1.0$ M. The K's were much greater than before (cf. Tables I and II; previous values were, malononitrile, ca. 10 M^{-1}, and fumaronitrile, 3.0 M^{-1}) and $\delta_c - \delta_a$ values were much smaller.

Conceivably a further reduction in concentration would further increase the K's. Evidence that this might *not* be so was obtained for malononitrile by measuring K_2 and using it to estimate the concentration of 2:1 complex in dilute solutions. A K value of 60 M^{-1} (Table I) implies that at 1.0 M HMPA, 0.1 M malononitrile is ca. 98% complexed. Using δ_c measured for the 1:1 complex as "δ_a" for the 2:1 complex, data for four points from 1.29 to 3.06 M HMPA gave a linear plot and $K_2 = 0.20 \pm 0.01$ M^{-1};[8] denoting the chemical shift of the 2:1 complex as δ_c', $\delta_c' - \delta_c$ was 1.8 ppm. From these values of K_1 and K_2 we estimate that at 1.0 M HMPA and ca. 0.1 M malononitrile, about 20% of the donor is present as 2:1 complex, but less than 2% at 0.1 M HMPA and 0.02 M malononitrile.

Measured Formation Constants. Tables I and II present data for C(sp^3)–H donors and for C(sp^2)–H and C(sp)–H donors, respectively, all with HMPA in CCl_4 at 35 °C. Table III presents data for a few donors with acceptors other than HMPA. Figures 1 and 2 show Higuchi plots for several representative donors with HMPA in CCl_4, having either high or low K values. As noted above, linearity is excellent, although some scatter is evident when K is low. Standard deviations determined in several cases are included in Tables I–III. A more crucial measure of precision is of course the reproducibility of the K values. Three separate runs with Br_2CHCN and two runs with chloroform, shown in Table I, gave such

Table I. Formation Constants of C(sp^3)–H Donors with HMPA in CCl_4 at 35 °C

Registry no.	Donor, AH	[AH], M	Range of [HMPA], M	No. of points	$\delta_c - \delta_a$ obsd, ppm	K, M^{-1}	$-\Delta\bar{\nu}$, cm^{-1}
67-66-3	$HCCl_3$	0.03	0.03–0.3	7	1.79	2.35	29[a]
		0.10	0.5–1.5	3	1.83	2.12	
75-25-2	$HCBr_3$	0.10	0.1–0.8	7	1.71	2.0	50[a]
75-95-6	Br_3CCHBr_2	0.10	0.2–0.9	7	1.81	1.12 ± 0.03	58[a]
74-95-3	CH_2Br_2	0.10	0.2–1.5	7	0.77	0.68	3, 11[a]
618-31-5	$C_6H_5CHBr_2$	0.11	0.2–1.0	6	1.60	0.68 ± 0.03	
619-75-0	p-$O_2NC_6H_4CHBr_2$	0.10	0.2–1.2	7	1.33	5.54 ± 0.15	
359-12-6	F_2CHCN	0.13	0.2–1.0	7	1.25	10.7	0
3018-12-0	Cl_2CHCN	0.12	0.1–0.8	7	2.08	20.6 ± 1.1	66
3252-43-5	Br_2CHCN	0.09	0.1–1.0	7	2.21	17.3	80[a]
		0.10	0.1–1.0	5	2.23	16.0	
		0.23	0.2–1.2	7	2.22	16.2	
107-14-2	$ClCH_2CN$	0.03	0.05–0.3	7	0.76	4.6	15[a]
4553-07-5	$C_6H_5CH(CN)CO_2Et$	0.05	0.2–1.6	7	1.70	1.30	
109-77-3	$CH_2(CN)_2$	0.02	0.03–0.14	7	0.98	60.0 ± 0.6	45, 75[b]
1885-22-9	$BrCH(CN)_2$	0.05	0.08–0.3	7	2.86	205	123
598-91-4	Br_2CHNO_2	0.25	0.1–1.0	6	1.98	10.3	80
611-38-1	$C_6H_5CH(NO_2)_2$	0.03	0.03–0.27	6	1.88	28.8	0
5468-76-8	$Cl_2CHCONMe_2$	0.09	0.1–1.0	4	1.48	1.44 ± 0.01	
116-54-1	Cl_2CHCO_2Me	0.08	0.1–1.0	4	1.75	0.68 ± 0.02	26[a]
6317-18-6	$CH_2(SCN)_2$	0.05	0.4–0.7	4	0.875[c]	8.2 ± 0.6[c]	15
6262-51-7	c-C_3HCl_5	0.10	0.2–1.0	7	3.00	0.59 ± 0.03	88[a,d]

[a] Reference 3. [b] C–H stretch band a doublet in pure $CDCl_3$, but broad singlet in presence of Me_2SO-d_6. [c] In CS_2; donor insoluble in CCl_4; in CS_2, Br_2CHCN had K = 20.7 ± 1.6 M^{-1}. [d] Pyridine-d_5 as acceptor.

Table II. Formation Constants of C(sp^2)–H and C(sp)–H Donors with HMPA in CCl_4 at 35 °C

Registry no.	Donor, AH	[AH], M	Range of HMPA, M	No. of points	$\delta_c - \delta_a$, obsd, ppm	K, M^{-1}	$-\Delta\bar{\nu}$, cm^{-1}
598-16-3	$Br_2C{=}CHBr$	0.1	0.2–1.5	5	2.20	0.23	40[a]
79-01-6	$Cl_2C{=}CHCl$	0.1	0.2–1.4	7	2.70	0.27	41[a]
764-42-1	E-NC-CH=CHCN (fumaronitrile)	0.015	0.04–0.25	7	0.90	14.5	45
123-06-8	$C_2H_5OCH{=}C(CN)_2$	0.05	0.2–1.0	7	1.38	18.1	55
4786-24-7	$(CH_3)_2C{=}CHCN$	0.2	0.5–2.0	4	0.90	0.26	
1885-38-7	E-$C_6H_5CH{=}CHCN$ (α)	0.1	0.5–2.0	5	1.10	1.24	
				7	1.13	1.12	
5153-67-3	E-$C_6H_5CH{=}CHNO_2$ (α)	0.1	0.5–2.0	7	0.97	1.06	
	E-$C_6H_5CH{=}CHCN$ (β)	0.1	0.5–2.0	5	0.32	0.66	
				7	0.18	1.25	
	E-$C_6H_5CH{=}CHNO_2$ (β)	0.1	0.5–2.0	4	0.36	1.24	
108-70-3	1,3,5-$C_6H_3Cl_3$	0.25	0.2–3.0			*b*	27
95-94-3	1,2,4,5-$C_6H_2Cl_4$	0.25	0.5–1.5	4	2.20	0.073	40[a]
	1,2,4,5-$C_6H_2Cl_4$	0.1	0.7–1.8	5	1.02[c]	0.59[c]	40
608-93-5	C_6HCl_5	0.05	0.7–2.0	4	3.07	0.092	
				5	3.40	0.085	
	C_6HCl_5	0.05	0.5–2.0	7	1.57[c]	0.69[c]	
				5	1.60[c]	0.66[c]	
117-18-0	3-NO_2-1,2,4,5-C_6HCl_4	0.05	0.1–1.0	6	1.81	0.49	45[a,d]
327-54-8	1,2,4,5-$C_6H_2F_4$	0.05	0.3–1.0	5	1.27	0.45 ± 0.01	50
	1,2,4,5-$C_6H_2F_4$	0.025	0.1–0.3	3	1.11[c]	2.58[c]	50
917-92-0	t-BuC≡CH	0.1	0.2–2.0			*e*	82[a,f]
536-74-3	$C_6H_5C{\equiv}CH$	0.23	0.25–1.7	7	4.0	0.15 ± 0.02	105
106-96-7	$BrCH_2C{\equiv}CH$	0.08	0.6–1.4	5	2.09	0.53 ± 0.01	102[a]
623-47-2	$C_2H_5O_2CC{\equiv}CH$	0.1	0.3–0.85	4	2.69	1.66 ± 0.02	
1070-71-9	$NCC{\equiv}CH$	0.08	0.3–1.0	7	3.08	12.1 ± 0.6	155

[a] Reference 3. [b] Too small to measure; plot scattered. [c] In cyclohexane solvent. [d] With 2 M pyridine-d_5 in CCl_4. [e] Too small to measure; Higuchi plot had negative slope. [f] Reported for 1-hexyne.

good agreement that runs with other compounds were not repeated unless the Higuchi plot showed excessive scatter or curvature.

Inspection of the K values of Tables I–III reveals several regularities. Chloroform and bromoform have nearly equal constants, as reported previously for THF in cyclohexane;[4] the three dihalonitriles studied also have similar K's within a factor of 2. All the nitriles have sizable K's, as do both nitro compounds of Table I. The constant for bromomalononitrile is the largest one known to us for C–H bonds, and is consistent with K's for other α-bromo and α-cyano compounds. Trichloro- and tribromoethylene have similar K's.

Substituent effects in the sp^3 series are consistent, since the effects of substitution of certain groups for others, evaluated

Table III. Formation Constants with Various Acceptors and Solvents at 35 °C

Donor	Acceptor	Solvent	No. of points	$\delta_c - \delta_a$, ppm	K, M^{-1}
$HCCl_3$	HMPA	CCl_4	7	1.79	2.35
	HMPA	c-C_6H_{12}	7	1.90	12.0
$HCCl_3$	Me_2SO	CCl_4	7	1.01	0.94
Br_2CHCN	HMPA	CCl_4	5–7	2.22[a]	16.5[a]
Br_2CHCN	Me_2SO	CCl_4	5	1.26	5.58
Br_2CHCN	DMF	CCl_4	7	1.23	3.59
Br_2CHCN	HMPA	c-C_6H_{12}	6	2.39	70.6
Br_2CHCN	HMPA	CS_2	7	2.22	20.7
Br_2CHCN	HMPA	Benzene	6	4.50	6.20
$CH_2(CN)_2$	HMPA	CCl_4	7	0.98	60
$CH_2(CN)_2$	Acetone	CCl_4	6	0.48	3.39 ± 0.04
$CH_2(CN)_2$	DMF	CCl_4	3	0.56	11.4 ± 0.23
$C_6H_5CH(CN)_2$[b]	Acetone	CCl_4	4	0.92	1.70 ± 0.03
$C_6H_5CH(CN)_2$[b]	DMF	CCl_4	6	1.25	5.28
$C_6H_5CH(NO_2)_2$	Acetone	CCl_4	7	0.89	1.69 ± 0.02

[a] Mean of three runs; cf. Table I. [b] Registry no., 3041-40-5.

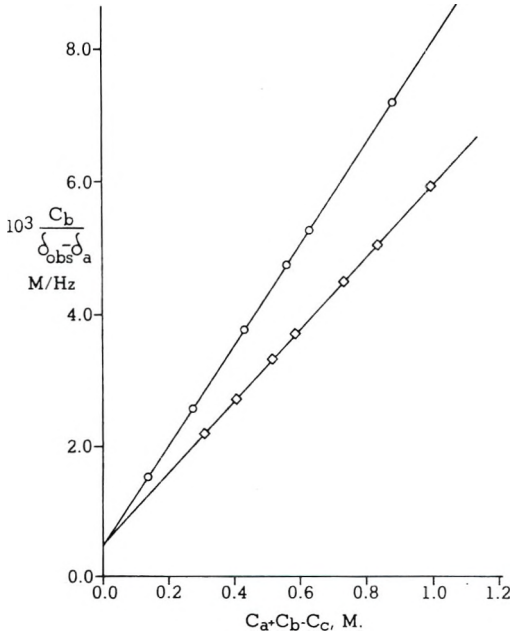

Figure 1. Higuchi plots for "strong" donors with HMPA in CCl_4, 35.0 °C: ○, Br_2CH-CN, c 0.09 M; ◇, H-C≡C-CN, c 0.08 M. The coincidence of the intercepts is not significant.

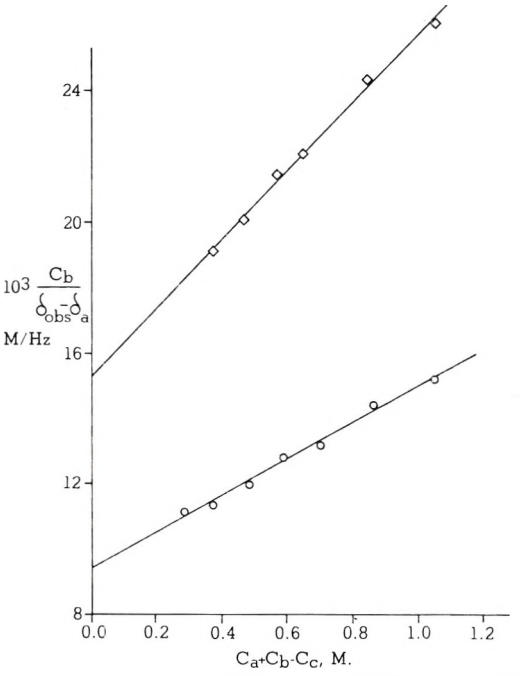

Figure 2. Higuchi plots for "weak" donors with HMPA in CCl_4, 35.0 °C: ○, pentachlorocyclopropane, c 0.10 M; ◇, $PhCHBr_2$, 0.11 M.

in more than one way and tabulated in Table IV, are in fair to good agreement. In these comparisons, $ClCH_2CN$ is used as a model for $BrCH_2CN$, as justified by the similarities of other Cl–Br analogues; K is divided by two for disubstituted methanes to correct for the presence of two C–H bonds.

Certain regularities in $\delta_c - \delta_a$ values also appear: thus, for dibromomethane, the observed value of 0.77 ppm is essentially one-half of that for benzal bromide ($C_6H_5CHBr_2$), 1.60 ppm, as expected if only one of the two protons of the former is complexed and if the effect of phenyl on δ_c is the same as on δ_a. (The dibromomethane experiment was not repeated at lower concentrations, as K was much smaller than for malononitrile.) A similar relationship holds for malononitrile and phenylmalononitrile with both acetone and DMF as acceptors. (We were unable to measure K for phenylmalononitrile and HMPA, as the proton resonance always broadened and disappeared in the presence of HMPA. A small amount of proton transfer, forming ion pairs, may have taken place at a net rate comparable to the relaxation time.)

Our results can be compared with previously reported results of other workers evidently only in the single case of chloroform–HMPA. Drago and co-workers[9] report K = 15.0 M^{-1} at 29.0 °C in cyclohexane. Extrapolation to 35.5 °C using $\Delta H°$ = −5 kcal/mol gives K = 13.0 M^{-1}. We subsequently obtained K = 12.0 M^{-1}, in good agreement, and $\delta_c - \delta_a$ = 1.90 ppm, in excellent agreement with 1.92 ppm reported by Drago et al. The anomalously large value of K in cyclohexane as compared to CCl_4 has now been observed for several donors of widely differing K's, and is under investigation.

Discussion

The data presented in Tables I–III contain enough regularities to inspire confidence in their validity, but they contain several significant surprises. The ensuing discussion will focus exclusively on equilibrium constants, in which we are principally interested. Absolute values of $\delta_c - \delta_a$ are of unknown significance at this point, except for a crude trend to higher values where K values are large.

Formation Constants and Infrared Shifts. First, our results confirm our previous observation that K and $-\Delta\bar{\nu}$ are not correlated for C–H bonds generally, and only vaguely within a group, e.g., the C(sp^3)–H series. Two donors with

Table IV. Effect of Substituent Changes on K for C(sp^3)–H Systems

New group	Group replaced	Compds compared	K values[a]	Ratio of K's
CN	Br or Cl	$CH_2(CN)_2/ClCH_2CN$	30./2.3	13.0
CN	Br or Cl	$Br_2CHCN/HCBr_3$	16.5/2.0	8.3
CN	Br or Cl	$BrCH(CN)_2/Br_2CHCN$	205/16.5	12.4
Br	H	$Br_2CHCN/ClCH_2CN$	16.5/2.3	7.2
Br	H	$BrCH(CN)_2/CH_2(CN)_2$	205/30.	6.8
Br	H	$HCBr_3/CH_2Br_2$	2.0/0.34	5.9
CN	H	$BrCH(CN)_2/ClCH_2CN$	205/2.3	89
CN	H	Br_2CHCN/CH_2Br_2	16.5/0.34	49
NO_2	H	Br_2CHNO_2/CH_2Br_2	10.3/0.34	30

[a] Cf. Table I.

large K's, F_2CHCN and $PhCH(NO_2)_2$, have $-\Delta\bar{\nu} = 0$; phenylacetylene and pentachlorocyclopropane have small K's but large values of $-\Delta\bar{\nu}$. Bromomalononitrile, with the largest K, 205 M^{-1}, has a smaller $-\Delta\bar{\nu}$ than cyanoacetylene, $K = 12\ M^{-1}$, although the latter value is large for an acetylene. Figure 3 is a plot of log K vs. $-\Delta\bar{\nu}$ for the C(sp^3)–H donors studied; it is little better than a scatter diagram in which scarcely any trend is discernible. Factors which perturb the C–H bond and cause the observed shift must be related in a complex way to those which determine $-\Delta F°$, i.e., log K. It is clear that infrared shifts may not be used to make predictions about the magnitude of the formation constant.

Correlations of thermodynamic parameters with ir shifts were evidently first suggested by Badger and Bauer,[10] who did not expect generality. Subsequent work has confirmed such skepticism while revealing many examples of good correlations for limited ranges of donors or acceptors or both.[11] Several factors must contribute to the lack of correlation for C–H donors. One is that changes in the structure of the donor occur closer to the C–H bond than to the O–H bond in systems such as substituted phenols. Another is a fundamental difference between the ir and NMR methods: the ir shift is characteristic of a species of very definite structure (A–H and H–B distances and A–H–B angle), while the NMR measurement takes into account all possible interactions between A–H and B.

Substituents and Formation Constants. The effect of substituents on formation constants is qualitatively similar for the three main classes of C–H bonds, i.e., independent of hybridization. Thus, for the C(sp^3)–H series, the order is CN $\simeq$ NO_2 > SCN, p-O_2N-C_6H_4 > F, Cl, Br > $CONMe_2$ > CO_2R $\geq$ C_6H_5. This order is followed also in sp^2 and sp systems which have thus far been studied. The failure of K for Cl_2CHCO_2Me to rival that for Cl_2CHCN, or even greatly to exceed that for CH_2Br_2, was particularly unexpected.

These substituent effects are worth examining, since they may shed some light on the nature of the C–H H bond. We shall adopt a working model of the H bond which is consistent with the bulk of theoretical work carried out in recent years and discussed by, among others, Coulson,[12] Murrell,[13] and Kollman and Allen.[14] In valence bond terms, at least three structures, **1–3**, contribute to the H bond. Electrostatic attraction is represented by **2**, while **3** illustrates charge transfer. Repulsive and dispersion contributions are also important but are not represented by distinct structures here. The view is generally held that **2** is the dominant attractive contribution to weak, long H bonds. Structure **3** becomes important for stronger, shorter H bonds. Valence bond theory thus suggests localization of electrons on A, and results of MO calculations strongly support this view. According to Kollman and Allen,

$$\underset{1}{A{-}H\cdots:B} \longleftrightarrow \underset{2}{A:^{-}\ \overset{+}{H}\ :B} \longleftrightarrow \underset{3}{A:^{-}\ H{-}B^{+}}$$

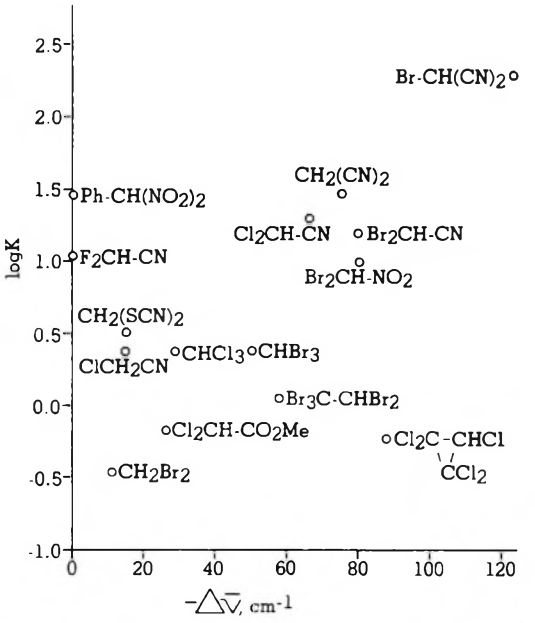

Figure 3. Relation between donor–HMPA formation constants (K's) and infrared C–H stretching wavenumber shifts.

both B and A gain electrons, while H loses electrons; the gain by A is greater than that of B; atoms attached to B lose electrons, while those attached to A gain electrons. Apparently the only C–H system mentioned by Kollman and Allen is HCN: its dimer is said to have a long H bond (3.2 Å), for which the electrostatic model should work well.

Substituent effects on C–H H bonding can evidently arise in several ways: (1) interaction with the charge generated on A, which may be subdivided into field, σ-inductive, and delocalization (resonance) components; (2) electrostatic attraction between the electronegative B and the electropositive end of the substituent; (3) steric interference between B and bulky substituents on A.

It is doubtful that resonance effects in A–H are very significant.[32] If they were, the substituent order would more nearly resemble that in Bronsted acidity, in which lone pairs are fully formed and the effect of substituents may largely be explained by delocalization. In carbon acidity, NO_2 is much more effective than CN, and CO_2R only slightly less effective than CN. Thus, in aqueous solution, nitromethane and dinitromethane have pK_a's of ca. 10 and 4, respectively, while that of acetonitrile is estimated to be 25, of malononitrile 12, and diethyl malonate ca. 13.3.[15] Not too surprisingly, this suggests that in C–H H bonding the degree of charge redistribution toward carbon is modest.

The two principal nonconjugative effects, the σ-inductive and field effects,[16] are probably important in C–H H bonding. The separation of these effects has never been achieved;[16b] although there is conclusive evidence for the field effect[16c] and fairly good evidence for the σ-inductive effect, disagreements have arisen as to their relative importance.[17] Both effects are probably encompassed by the most successful measure of nonconjugative polar effects, the Taft σ_I constants.[18] These fall in the order Me_3N^+ > NO_2 > CH_3SO_2, CN > F, Cl, Br > I, OC_6H_5, CF_3 > CO_2Et, COMe > OCH_3, C_6H_5, which agrees with the H-bonding order with respect to CN vs. both NO_2 and carbonyl substituents. However, this correlation is qualitative, not quantitative, as shown by the scatter in Figure 4, a plot of log K vs. the sum of the σ_I constants for C(sp^3)–H donors. A line through the points for the dibromo- and dichloroacetonitriles, dibromomethane, and α,α-dibromotoluene gives a ρ value of ca. +2.7. It is noteworthy that other systems fail to correlate with σ_I, e.g., the substituent chemical shifts in ^{19}F

NMR spectra of maleic anhydride adducts of 10-substituted 9-fluoroanthracenes.[19]

The failure of the Taft correlation to be quantitative may be attributed to several causes. The first is that steric effects are important. This would account for several of the points in Figure 4 falling below the arbitrary line mentioned above. Second, there may be a different blend of σ-inductive and field effects than in the reactions used to define σ_I, and substituents may differ in their effectiveness by the two mechanisms. One theoretical conclusion given above, viz., that substituents on A gain electrons, is compatible with the σ-inductive effect in that gain of electrons by an electronegative group is energetically favorable. A third possible reason for failure of the correlation might be the increasing importance of charge transfer for the strongest C–H donors. A final and more troublesome reason is the fact that the NMR method measures all modes of interaction of A–H and B, not just those giving a linear, three-center hydrogen bond. The possible interactions may clearly vary uncontrollably with the substituent.

Substituent Effects in Unsaturated Donors. Substituent effects in the sp^2 and sp series are quite large, although we cannot yet evaluate these in as much detail as for the sp^3 series. Replacement of three halogens in the trihaloethylenes by two nitrile groups increases K by 54- to 63-fold. The size of K for fumaronitrile suggested study of analogues with only one cyano group, as well as a compound with a vinylic nitro group. From the K's for β,β-dimethylacrylonitrile ($Me_2C{=}CHCN$) and the α proton of (*E*)-cinnamonitrile (PhCH=CHCN), one can see that the second cyano group of fumaronitrile is an important contributor to the size of its K (7.2 M^{-1} per proton). This is also evident from the large K of 18.1 M^{-1} for ethoxymethylenemalononitrile [EtO-CH=C(CN)$_2$], which has only β-cyano groups. The effect of the nitro group in (*E*)-β-nitrostyrene ($PhCH{=}CHNO_2$) on the α proton is essentially identical with that of cyano in (*E*)-cinnamonitrile, consistent with results in the C(sp^3)–H series. The β-phenyl group evidently has a significant K-enhancing effect in both compounds, relative to β,β-dimethyl substitution in β,β-dimethylacrylonitrile. The results for the β protons of both cinnamonitrile and β-nitrostyrene are intriguing, both in the sizable K's and the very small values of $\delta_c - \delta_a$. A study of the stereochemistry of the β-substituent effect, utilizing the *Z* isomers, as well as angelo- and tiglonitriles (*E*- and *Z*-MeCH=CMeCN, respectively) would be of interest, but the small shifts would complicate the interpretation.

The aromatic compounds studied provide good examples of the poor predictive powers of ir shifts, in view particularly of our failure to measure K for 1,3,5-trichlorobenzene. Even the K's for 1,2,4,5-tetrachlorobenzene and pentachlorobenzene in CCl_4 are questionable since the $(\delta_c - \delta_a)$'s are more than twice as large as the values obtained in cyclohexane. Use of cyclohexane as solvent (vide supra) rendered these K's readily measurable, and revealed the substituent effect orders 4-NO_2 > 4-Cl, and 1,2,4,5-F_4 > 1,2,4,5-Cl_4. One would thus expect 1,3,5-trinitrobenzene to show a sizable K, but curiously the chemical shift of its protons moves to *higher* field, rather than lower, in HMPA relative to CCl_4. We are currently investigating methylated analogues, e.g., TNT, to gain insight into this anomaly.

The effects of substituents on K's for acetylenes are particularly impressive when one considers that only β substituents are possible, and only one of these. Replacement of phenyl by cyano increases K by nearly 100-fold, by carboethoxy, 11-fold, and even by γ-bromine, by threefold. From the fact that K for *tert*-butylacetylene was too small to measure, a phenyl group is K enhancing relative to alkyl. These observations are in quantitative contrast to those for C(sp^3)–H donors, and suggest that electrical effects are more effectively transmitted through a triple bond than a single bond. This is consistent with the greater polarizability of π than σ electrons, and suggests operation of the π-inductive effect, recently demonstrated by Fukunaga and Taft.[20] Although the π orbitals are of course orthogonal to the C–H bonding orbital, polarization of π electrons toward the substituent would reduce the net charge developed at the carbon atom by H bonding.

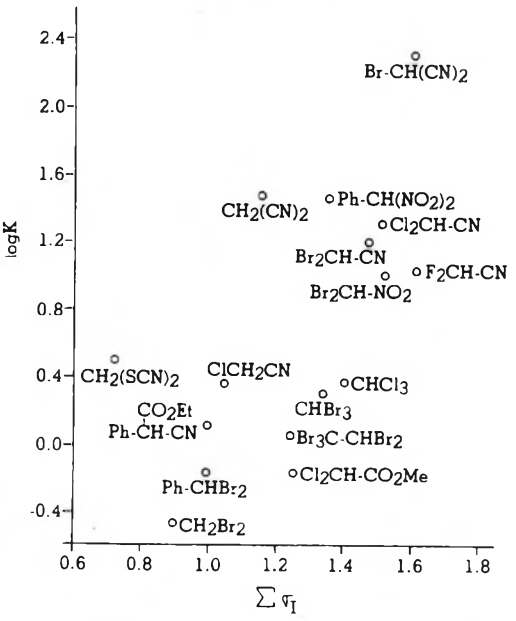

Figure 4. Relation between K's and sum of Taft σ_I values (cf. ref 18).

Measurement of Small *K*'s. We close with mention of the problem that certain K's proved too small to measure by means of our materials and techniques. One solution would be to find another acceptor even stronger than HMPA. Although tetraalkylammonium chlorides and bromides have much larger ir shifts than Me_2SO,[21] the measured K's for chloroform with quaternary ammonium halides are reported to be nearly the same as for chloroform with HMPA.[22]

Another approach to measurement of small K's is the method of Homer et al.,[23] who used Benesi and Hildebrand's data treatment method[24] to obtain K's at acceptor mole fractions approaching unity. Such conditions eliminate uncertainties due to variation of bulk susceptibility with changing acceptor concentration. The method would be inapplicable to strong donors, which approach complete complexing at high acceptor concentration. Finally, the ir method may meet with greater success than NMR because of its greater sensitivity to low concentrations of complexed species, as well as its specificity to H bonding and freedom from the bulk anisotropy problem.

Experimental Section

Materials. Carbon tetrachloride and cyclohexane, reagent grade, were stored over Linde Type 4 molecular sieves. Hexamethylphosphoramide (HMPA), Aldrich Chemical Co., was generally used as received; for a few experiments it was vacuum distilled from benzenepentacarboxylic acid to remove any dimethylamine present; its water content was shown by Karl Fischer titration to be less than 6 mol %.[25] Most C–H donors were purchased as reagent grade materials and were used as received. Benzal bromide, $PhCHBr_2$, Aldrich, fumed in air; it was washed with aqueous sodium bicarbonate, then water, dried, and vacuum distilled before use. On standing a few days, it fumed again. Methylene bisthiocyanate, $CH_2(SCN)_2$, was kindly donated by the Stauffer Chemical Co.

Several nitriles were prepared by dehydration of the corresponding amides with P_2O_5; those amides not available commercially were prepared from the acid chlorides or methyl or ethyl esters. Difluoro-, dichloro-, and chloroacetonitriles and phenylmalononitrile were

prepared in this way; their boiling or melting points agreed with reported values, and spectral data supported the assigned structures. Bromomalononitrile was prepared by the method of Freeman,[26] mp 64.8–65.2 °C (lit.[26] 64.5–65.1 °C). Dibromonitromethane was prepared by two-stage bromination of nitromethane,[27] bp 60 °C (13 Torr) [lit.[28] 52 °C (16 Torr)]. Phenyldinitromethane was prepared by oxidative nitration[29] of phenylnitromethane (α-nitrotoluene, K & K Chemicals); it had mp 75–77 °C (lit.[30] 78–80 °C). Pentachlorocyclopropane was prepared from trichloroethylene and dichlorocarbene (from sodium trichloroacetate) as described by Tobey and West,[31] bp 55 °C (10 Torr) [lit.[31] 56 °C (7 Torr)].

Infrared Spectra. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer, wavenumber accuracy ca. ±5 cm^{-1}, calibrated vs. polystyrene film. Values of $\bar{\nu}$ were measured for ca. 0.1 M solutions in CCl_4 or $CDCl_3$ and again in the same solvent containing 1.0 M dimethyl sulfoxide-d_6. Cells, with NaCl windows, had path length either 1.0 mm, as used by Allerhand and Schleyer,[3] or 0.5 mm, and were well matched.

NMR Measurements. Solutions were prepared in 2-ml volumetric flasks by weighing the donor and acceptor, adding several drops of Me_4Si, and adding solvent to the mark. Some compounds, e.g., bromomalononitrile, were decomposed by neat HMPA; decomposition was prevented by adding ca. 1 ml of CCl_4 to the weighed donor before weighing the HMPA. Solutions were transferred to NMR tubes which were immediately stoppered and measurements were made within a few hours.

All chemical shifts were measured using a Varian T-60 spectrometer, probe temperature 35.5 °C, equipped with internal lock, Hewlett-Packard test oscillator Model 650A, and Beckman counter and timer Model 6155A. Me_4Si was employed for the lock signal. For each sample, the donor peak was centered on 100-Hz sweep width, the oscillator tuned to give a Me_4Si sideband null pattern first at the low field end of the scale, then at the high field end, and the period (1/frequency) of each pattern recorded. The chemical shift was calculated by solving a proportion among the frequencies of the null patterns and the distances between patterns and sample signal on the paper.

Formation Constants. These were calculated by the method of Higuchi et al.,[7] as outlined in the text. Least-squares refinement of plots for each iteration was aided by a Hewlett-Packard programmable calculator; iteration was carried out until $\delta_c - \delta_a$ was constant within ±0.1 Hz, not more than five cycles usually being required. Some data have also been treated using a FORTRAN IV program written by J.M.T. The resulting points were plotted; those points which were more than two standard deviations from the least-squares line were rejected; and the calculation was repeated. In most cases only one or two points of seven were rejected; with phenyldinitromethane one point diverged slightly from the line, the others appearing to lie precisely on the line. Points tended to scatter more the smaller K was; with 1,3,5-trichlorobenzene scatter was so severe as to permit values of K over a range of severalfold; with *tert*-butylacetylene the slope of the plot was negative (cf. text).

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References and Notes

(1) Taken in part from the M.S. Thesis of F.M.S., Central Michigan University, 1973.
(2) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond", W. H. Freeman, San Francisco, Calif., 1960, pp 197–201.
(3) A. Allerhand and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **85**, 1715 (1963).
(4) (a) C. J. Creswell and A. L. Allred, *J. Am. Chem. Soc.*, **85**, 1723 (1963); (b) B. B. Howard, C. F. Jumper, and M. T. Emerson, *J. Mol. Spectrosc.*, **10**, 117 (1963); (c) A. L. McClellan, S. W. Nicksic, and J. C. Guffy, *ibid.*, **10**, 340 (1963); (d) J. A. Bell and W. H. Snider, *J. Chem. Educ.*, **44**, 200 (1967); (e) T. J. V. Findlay, J. S. Keniry, A. D. Kidman, and V. A. Pickles, *Trans. Faraday Soc.*, **63**, 846 (1967); (f) S. Nishimura, C. H. Ke, and N. C. Li, *J. Phys. Chem.*, **72**, 1297 (1968); (g) Y. H. Shaw and N. C. Li, *Can. J. Chem.*, **48**, 2090 (1970); (h) P. Laszlo, *Prog. Nucl. Magn. Reson. Spectrosc.*, **2**, 231 (1967).
(5) (a) M. M. Kreevoy, H. B. Charman, and D. R. Vinard, *J. Am. Chem. Soc.*, **83**, 1978 (1961); (b) M. Goldstein, C. B. Mullins, and H. A. Willis, *J. Chem. Soc. B*, 321 (1970).
(6) J. P. Lorand, Q. A. Ahmed, and D. Hadler, paper presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, Abstract No. CRGN-58.
(7) M. Nakano, N. I. Nakano, and T. Higuchi, *J. Phys. Chem.*, **71**, 3954 (1967).
(8) K_2 is defined for the reaction AH·B + B = AH·B_2, rather than for AH + 2B = AH·B_2, for convenience. For the latter, $K = K_1K_2 = 12\ M^{-2}$.
(9) F. Slejko, R. S. Drago, and D. G. Brown, *J. Am. Chem. Soc.*, **94**, 9210 (1972).
(10) R. M. Badger and S. H. Bauer, *J. Chem. Phys.*, **5**, 839 (1937).
(11) (a) Reference 2, pp 82–85; (b) S. N. Vinogradov and R. H. Linnell, "Hydrogen Bonding", Van Nostrand-Reinhold, Princeton, N.J., 1971, p 138 ff; (c) M. D. Joesten and L. J. Schaad, "Hydrogen Bonding", Marcel Dekker, New York, N.Y., 1974, p 208 ff; (d) E. M. Arnett, L. Joris, E. Mitchell, T. S. S. R. Murty, T. M. Gorrie, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **92**, 2365 (1970); (e) E. M. Arnett, E. J. Mitchell, and T. S. S. R. Murty, *ibid.*, **96**, 3875 (1974).
(12) C. A. Coulson, *Research*, **10**, 149 (1957); cited in ref 11c.
(13) J. N. Murrell, *Chem. Br.*, **5**, 107 (1969).
(14) P. A. Kollman and L. C. Allen, *Chem. Rev.*, **72**, 283 (1972).
(15) D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, N.Y., 1965, pp 10–12.
(16) (a) J. Hine, "Physical Organic Chemistry", 2d ed, McGraw-Hill, New York, N.Y., 1962, pp 60–63; (b) S. Ehrenson, *Prog. Phys. Org. Chem.*, **2**, 195 (1964); (c) H. D. Holtz and L. M. Stock, *J. Am. Chem. Soc.*, **86**, 5188 (1964); (d) R. W. Taft and C. A. Grob, *ibid.*, **96**, 1236 (1974).
(17) (a) M. J. S. Dewar, R. Golden, and J. M. Harris, *J. Am. Chem. Soc.*, **93**, 4187 (1971); (b) S. K. Dayal, S. Ehrenson, and R. W. Taft, *ibid.*, **94**, 9113 (1972).
(18) (a) J. March, "Advanced Organic Chemistry", McGraw-Hill, New York, N.Y., 1968, p 243. (b) For –SCN, only σ_p is apparently reported; a value of +0.36 for σ_I is estimated from calculations by Charton;[18c] judging from Figure 4, this may be too small. (c) M. Charton, *J. Org. Chem.*, **28**, 3121 (1963).
(19) G. L. Anderson and L. M. Stock, *J. Am. Chem. Soc.*, **90**, 212 (1968).
(20) J. Fukunaga and R. W. Taft, *J. Am. Chem. Soc.*, **97**, 1612 (1975).
(21) A. Allerhand and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **85**, 1233 (1963).
(22) R. D. Green and J. S. Martin, *J. Am. Chem. Soc.*, **90**, 3659 (1968).
(23) J. Homer, C. J. Jackson, P. M. Whitney, and M. H. Everdell, *Chem. Commun.*, 956 (1971).
(24) H. A. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc.*, **71**, 2703 (1949).
(25) We are indebted to Mr. Jon Nelson for performing this experiment.
(26) F. Freeman, Ph.D. Thesis, Michigan State University, 1962, p 110; private communication from Professor H. Hart.
(27) R. Scholl, *Ber.*, **29**, 1822 (1896).
(28) H. Wieland and H. Jung, *Justus Liebigs Ann. Chem.*, **445**, 91 (1925).
(29) R. B. Kaplan and H. Schechter, *J. Am. Chem. Soc.*, **83**, 3535 (1961).
(30) L. F. Fieser and W. von E. Doering, *J. Am. Chem. Soc.*, **68**, 2252 (1946).
(31) S. W. Tobey and R. West, *J. Am. Chem. Soc.*, **88**, 2478 (1966).
(32) A referee has suggested that ion pairs may form in our systems to a minor extent, but making a major contribution to δ_{obsd}. While we have evidence of sorts for ion pairs with phenylmalononitrile–HMPA (vide supra), we would expect the general linearity of the Higuchi plots to have been destroyed by ion pair formation. We agree, however, that charge redistribution probably takes place within A–H···B.

Mixed Valence Cations. Chemistry of π-Bridged Analogues of Biferrocene and Biferrocenylene

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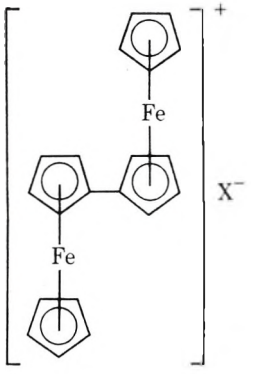
Solutions of the mono- and dications of acetylene bridged analogues of biferrocene and biferrocenylene were generated electrochemically in order to investigate their ESR and absorption spectra. The visible and near-infrared spectra of the mono- and dications of diferrocenylacetylene and diferrocenylbutadiyne show features similar to biferrocene cations. Moderately intense bands in the near-infrared spectra of the diferrocenylacetylene monocation (λ 1560 nm, ε 670) and the diferrocenylbutadiyne monocation (λ 1180 nm, ε 570) are assigned to intervalence transfer transitions. The energy of the bands increases as the iron–iron distance increases. A corresponding decrease in the intensity of the bands, and $\Delta E_{1/2}$, the separation in half-wave potentials, is observed. The opposite effect of frequency and intensity as a function of metal–metal distance is noted in the spectra of the ferrocenophane cations. The monocation of [2.2]ferrocenophane-1,13-diyne (FDA) has a near-infrared band (λ 1760 nm, ε 2100) at lower energy and higher intensity than the biferrocenylene (BFD) monocation. The ESR spectrum of FDA (2,3) has a rhombic *g* tensor and sharp lines, and bears strong resemblance to that of BFD (2,3). The electrochemical and spectral results suggest that FDA (2,3) is a delocalized analogue of the BFD cation.

The mixed valence monocations of biferrocene (I) and biferrocenylene (II) (bisfulvalenediiron, BFD) have been characterized by a variety of physical measurements.[1,2] A general property of mixed valence monocations is the appearance of low-energy transitions not found in either the neutral or dicationic species.[3,4] For both biferrocene (2,3) and BFD (2,3) salts,[5] such transitions are observed in the near infrared.[6,7,8] The similarity between these compounds, however, ends here. It has been shown that the relatively small structural change in going from biferrocene to biferrocenylene produces a drastic difference in the physical properties of the ions.



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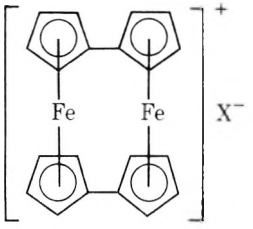
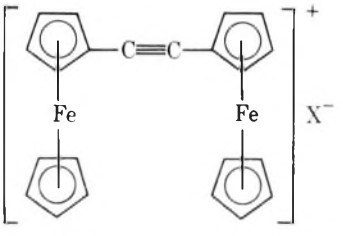


II (BFD)

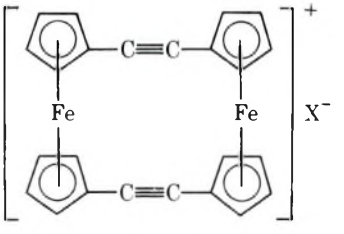
The biferrocene (2,3) ion has been described as a system in which there is only weak interaction between the two halves (i.e., the two iron atoms) in the ground state. Electron transfer is sufficiently slow to allow detection of signals ascribable to the ferrocene and ferrocenium portions of the molecule in Mossbauer[9] and ESCA[10] experiments. Likewise, the magnetic properties of I are reasonably well explained in terms of a perturbed ferrocenium ion.[11]

The BFD (2,3), however, defies these descriptions. Mossbauer and ESCA results[12] must be interpreted in terms of a fully delocalized system in which both iron atoms are equivalent. Because of this essential difference, it is likely that the near-infrared transition observed for BFD (2,3) cannot be explained by the simple model which has been applied successfully to the weakly interacting biferrocenes.[6,13] The question remains as to whether the delocalized nature of BFD (2,3) results from greater metal–metal interaction due to the proximity of the iron atoms in the forced cis conformation, or from interactions through the π system of the fused fulvalene ligands. In this study, an attempt is made to evaluate these factors.

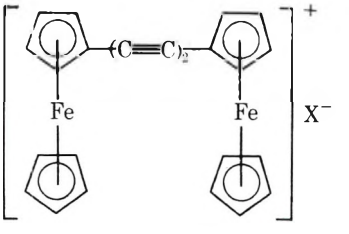
The cations of biferrocenes bridged by acetylene linkages, such as compounds III–V, provide a conjugated ligand system in which iron–iron distances (estimated to be 6.5 Å in IV) are too large to allow substantial direct metal–metal interaction. We recently reported[14] that the diferrocenylacetylene cation (III) exhibits a low-energy transition not observed in the (2,3) and (3,3) compounds. This intervalence transfer transition and the "ferrocenium" transition in the visible have energies and intensities on the order of those observed for biferrocene (2,3) cations.[13] If the metal centers in mixed valence ions can interact solely through the π system of planar ligands, we



III



IV (FDA)



V

might expect the bisacetylene bridged ferrocenophane cation [FDA (2,3), IV] to be a fully delocalized analogue of BFD (2,3). Herein we wish to report the results of electrochemical, ESR,

and electronic absorption studies which have bearing on this question.

Experimental Section

Materials. The neutral compounds, diferrocenylacetylene,[15] [2.2]ferrocenophane-1,13-diyne (FDA),[16] and 1,4-diferrocenylbutadiyne,[17] were synthesized by literature procedures. The preparations of the biferrocene (2,3) cation[6] and the BFD (2,3) cation[7,8] have been described. Ferrocenylacetylene was purchased from Wind River Chemicals. Spectrograde CH_2Cl_2 (Burdick and Jackson) was dried by passage through an alumina column (Woelm, activity I Basic), purged with argon, and stored in a sealed siphon bottle until used. The electrolyte, n-Bu_4NBF_4, was prepared[18] from n-Bu_4NHSO_4 (Aldrich) and vacuum dried.

Electrochemistry. Cyclic voltammograms were obtained using a PAR 175 Universal Programmer and a PAR 173 potentiostat combined with a standard three-electrode configuration. The working electrode, a platinum button (Beckman), and the reference, a saturated calomel electrode, were connected via a salt bridge containing n-Bu_4NBF_4 (0.2 M) in CH_2Cl_2. All electrochemical experiments were performed under argon. The current function, $[i_p/(V^{1/2}C)]$,[19] was constant over a wide range of sweep rates (25–300 mV/s), and a 1:1 relationship of the anodic and cathodic peak currents was observed. Together, these indicate the electrochemical reversibility of the couples. The half-wave potentials given in Table I were calculated from peak potentials.[19]

In preparative runs, 0.05 mmol of substrate was oxidized on a platinum basket in a cell holding 50–100 ml of solvent (0.1 M in electrolyte). Owing to the sparing solubility of neutral FDA, solutions of its cations were generated by controlled potential oxidation. The greater solubility of diferrocenylacetylene and diferrocenylbutadiyne permitted preparation of the cations by constant current oxidation. Samples for absorption spectra were transferred from the electrolysis cell through 2-mm Teflon tubing to a 1-cm quartz flow cell which was thoroughly rinsed with the electrolysis solution and then sealed by pinching the Teflon tubing. Visible and near-infrared spectra were recorded on a Cary 14 spectrophotometer within 15 min of sample preparation.

The FDA dication can be generated in CH_2Cl_2, but it is only slightly soluble. Attempts to record its spectrum in CH_2Cl_2/CH_3CN mixtures were unsuccessful owing to rapid decomposition to the monocation.

ESR. Samples for ESR measurements were transferred from the electrolysis cell to thin-walled Pyrex tubes. The solutions were degassed on a vacuum line by ten freeze–thaw cycles and sealed off. ESR spectra were recorded on a Varian E-12 spectrometer with 100-kHz modulation. The field was standardized by use of diphenyl picrylhydrazil at two different microwave frequencies.

Results and Discussion

Electrochemistry. Polyferrocenes and ferrocenophanes, like ferrocene itself, generally undergo reversible one-electron oxidations with the number of waves being determined by the number of ferrocenyl units.[20,21] The half-wave potentials of the redox processes and the separation between consecutive waves vary over a wide range depending on the nature of the compound. The half-wave potentials for formation of I–V as determined by cyclic voltammetry in CH_2Cl_2 containing n-Bu_4NBF_4 are given in Table I. The neutral compounds are reasonably soluble in this solvent/electrolyte system and the electrochemically generated mono- and dications are relatively stable.

The neutral compounds corresponding to I–V all undergo two successive reversible one-electron oxidations to yield the mono- and dications, respectively (eq 1)

$$\text{Fc—X—Fc} \overset{-e}{\rightleftarrows} [\text{Fc—X—Fc}]^+ \overset{-e}{\rightleftarrows} [\text{Fc—X—Fc}]^{2+} \quad (1)$$

(where Fc represents a ferrocenyl unit and X can be one or more bridging groups). Biferrocene, BFD, and FDA exhibit well-resolved one-electron waves. Diferrocenylacetylene and diferrocenylbutadiyne, however, owing to a relatively small difference ($\Delta E_{1/2}$) between the first and second half-wave potentials, show cyclic voltammograms characteristic of superimposed one-electron waves.[22] There is sufficient resolution in Fc—C≡C—Fc to assign peak potentials. For Fc(—C≡C—)$_2$Fc, these values are estimated, since only an inflection in the wave can be detected. That the butadiyne undergoes two one-electron processes, rather than a two-electron oxidation, is demonstrated by the difference in peak potentials (140 mV) of the oxidative and reductive peaks. For a two-electron oxidation, a difference of 30 mV is expected.[19]

Table I. Half-Wave Potentials[a] in CH_2Cl_2[b]

Compd	$E_{1/2}(1)$[c]	$E_{1/2}(2)$[c]	$\Delta E_{1/2}$[d]
Fc—C≡C—Fc	0.625	0.755	0.130
FDA	0.620	0.975	0.355
Fc(—C≡C—)$_2$Fc	~0.58	~0.68	~0.10
Biferrocene	0.435	0.785	0.350
BFD	0.265	0.855	0.590

[a] Calculated from peak potentials. [b] Containing n-Bu_4NBF_4 (0.2 M). [c] Volts vs. SCE at 100 mV/s (platinum disk electrode). [d] $\Delta E_{1/2} = E_{1/2}(2) - E_{1/2}(1)$.

The monocations III–V were generated from the neutral compounds by passage of precisely 1 F/mol. Exhaustive coulometric oxidation resulted in consumption of 2 F/mol and yielded the dications. Voltammetric and polarographic analyses of the resulting solutions indicated a current yield of 100%. Solutions of the monocations were stable for several days when protected from air and moisture. The dications, however, reverted to the monocations within a few hours.

Owing to the small difference between the first and second half-wave potentials of diferrocenylacetylene and diferrocenylbutadiyne, discrete solutions of the monocations III and V do not exist. An equilibrium mixture of three species is formed, as in eq 2:

$$2(2,3)^+ \rightleftarrows (2,2) + (3,3)^{2+} \quad (2)$$

When a solution of diferrocenylacetylene is oxidized by 1 F/mol, it is calculated, by use of the Nernst equation, that 90% of the species in the equilibrium mixture are the (2,3) monocations. For the butadiyne, with an estimated difference in half-wave potentials of 100 mV, only 70% of the species are the monocations V. This will probably preclude the isolation of the pure monocationic salts III and V, but their spectral properties can still be analyzed when the above ratios are taken into account.

A mixed valence compound can be characterized by an interaction parameter (α), which is proportional to the intensity of the intervalence transfer transitions, and reflects the extent of delocalization between iron centers in the ground state. Another measure of the degree of interaction between the halves of a biferrocene-type compound is $\Delta E_{1/2}$, the difference in half-wave potentials (Table I). It is tempting to try to correlate these parameters. Within a small series of structurally similar compounds, such as the acetylenes (III, V), such a correlation may be useful (vide infra). For the accumulated data on mixed valence biferrocenes with gross structural differences, however, no clear-cut interrelation between the magnitude of $\Delta E_{1/2}$ and the presence or absence of a low-energy band is substantiated. This can be seen from the following examples.

No intervalence transfer transitions have been observed in the near infrared for mixed valence biferrocenes bridged by sp^3 carbons. Such compounds are characterized by small $\Delta E_{1/2}$ values (0.17 V for $-CH_2-$ and 0.0 V for $-CH_2CH_2-$).[23] For selenium bridged biferrocenes, however, substantially larger potential differences are observed (0.22 V for –Se– and 0.14 V for –SeSe–), but again no low-energy transitions are found in the monocations.[24] The acetylene bridged cations III and

Table II. *g* Values for Mixed Valence Biferrocenyl Cations

Registry no.	Compd	Solvent	Temp, K	g_1	g_2	g_3
59187-96-1	FDA (2,3) BF_4	CH_2Cl_2[a]	77	1.88	1.98	2.57
39333-81-8	BFD (2,3) BF_4[b]	EtOH/CH_2Cl_2	160	1.87	2.00	2.27
				$g_\perp$	$g_\parallel$	
	FDA (2,3) BF_4	Solid[a]	77	1.94	2.70	
11108-35-3	Biferrocene (2,3) picrate[c]	Acetone	77	1.85	3.53	

[a] Containing n-Bu_4NBF_4. [b] Reference 2. [c] Reference 11.

V, on the other hand, have rather intense intervalence transfer bands and small $\Delta E_{1/2}$ values.

One trend that has been noted previously[21,23] is the increase in $\Delta E_{1/2}$ in doubly bridged ferrocenophanes as compared to the singly bridged derivatives. The size of $\Delta E_{1/2}$ approximately doubles when biferrocene is compared to BFD, diferrocenylacetylene to FDA, and diferrocenylmethane to [1.1]-ferrocenophane.[21] The exact cause of this increase in half-wave separation is unclear and may be due to elusive factors such as solvation energies, molecular size, and geometry, as well as orbital overlap between the two halves of the ferrocene molecule. At the present state of investigation, we find that intervalence transfer transitions occur only in biferrocenes that are directly fused or bridged by π-unsaturated groups, and occur regardless of $\Delta E_{1/2}$ values.

ESR. ESR spectra of ferrocenium ions have been interpreted in terms of an axial g tensor.[25] The spectra are characterized by large anisotropies and fast relaxation; the signals are detectable only at very low temperatures. The spectrum of mixed valence biferrocene (2,3) picrate showed similar features and was analyzed as a slightly perturbed ferrocenium ion.[11]

The spectrum of the BFD (2,3) ion, however, is quite different. The solid triiodide salt was found to have a rhombic g tensor and a relatively small anisotropy.[23] Furthermore, well-resolved spectra of the fluoroborate and picrate salts in glasses were obtained at temperatures higher than those suitable for substituted ferrocenium ions.[2] Exchange narrowing[23] and/or lower effective symmetry could give rise to the observed narrow lines.

The ESR spectrum of the FDA (2,3) cation has been measured in a methylene chloride glass at 77 K. Having a rhombic g tensor, and sharp lines, it bears strong resemblance to that of the BFD cation.[2] The g values are listed in Table II. The resolution of the glass spectrum is affected by trace amounts of oxygen, but reproducible results were obtained by careful degassing. Interestingly, the spectrum of solid FDA (2,3) BF_4 diluted in n-Bu_4NBF_4 (prepared by the evaporation of solvent from the electrolysis solution) shows axial symmetry, indicating that the solid may not be magnetically dilute.

Two different types of mixed valence biferrocenes have been distinguished by their magnetic properties: the weakly interacting biferrocene (2,3) cation, and the delocalized BFD (2,3) ion. Magnetically, the FDA (2,3) ion resembles the latter, which strongly suggests that FDA (2,3) should also be treated as a fully delocalized system. ESCA and Mossbauer experiments are necessary to verify this conclusion. It is, however, in accordance with the spectral similarities of the two compounds, as discussed below.

An attempt was made to obtain an ESR spectrum of the diferrocenylacetylene cation (III) under the experimental conditions described above. Only a very weak signal centered around $g = 2.00$ could be detected. We anticipated difficulty in obtaining the spectrum in light of the electrochemical results. The equilibrium mixture contains the dication which, if strongly paramagnetic, could affect the resolution drastically. No attempt was made to obtain the spectrum of V.

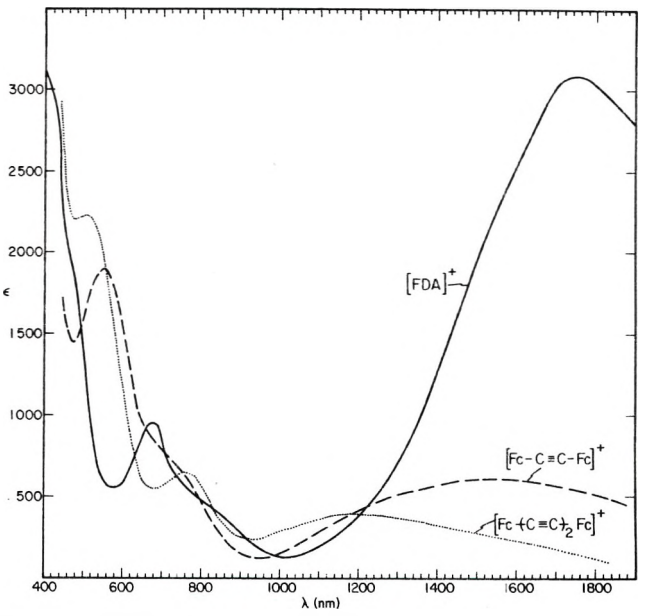


Figure 1. Visible and near-infrared spectra of the FDA monocation (IV) (—), the diferrocenylacetylene monocation (III) (- - -), and the diferrocenylbutadiyne cation (V) (· · ·) in CH_2Cl_2 containing 0.1 M n-Bu_4NBF_4.

Visible and Near-Infrared Absorption Spectra. The monocations I–V have low-energy transitions in the near infrared that are not found in their (2,2) and (3,3) derivatives. In addition, transitions in the visible are observed, similar to that found at 600 nm for the ferrocenium ion.[26,27] The visible and near-infrared spectra of cations III–V are shown in Figure 1. Table III lists the absorption maxima and intensities of the visible and near-infrared bands for several mono- and dicationic biferrocenes.

The 1800-nm band in biferrocene (2,3) has been assigned to an intervalence transfer transition[1] by which a vibrationally excited valence isomer is formed:

$$[\text{Fe(II)-Fe(III)}] \xrightarrow{h\nu} [\text{Fe(III)-Fe(II)}]^* \qquad (3)$$

A simple model for intervalence transfer transitions has been proposed by Hush.[3] The usefulness of this model in interpreting the results in a series of substituted biferrocenyl cations has been demonstrated.[13] The spectral results of the singly bridged acetylene cations III and V also appear to be consistent with this model.

In substituted biferrocenyl cations, the intensity of intervalence transfer transitions was shown to be dependent upon the overlap of π orbitals in the fulvalene ligand.[13] Mayoh and Day[29] have shown that in the absence of direct metal–metal overlap, the metal centers in mixed valence compounds can interact via ligand π and π^* orbitals. We might expect this mode of interaction to predominate in acetylene bridged biferrocene cations, owing to the large iron–iron distances. The intensities of the near-infrared bands in III and V are on the order of those observed for substituted biferrocenes. This gives some indication that similar processes of valence transfer might be involved in both the directly fused and acetylene bridged biferrocene cations.

In comparing the quantitative features of the near-infrared bands of I, III, and V, we find that the intensity decreases as the distance between the metal centers increases. Since the bandwidths are greater in both III and V (about 5000 cm^{-1})

Table III. Spectral Data

Registry no.	Compd	Solvent	λ_{max}, nm (ϵ) [a] Monocations	Dications
12098-14-5	Fc—C≡C—Fc	CH_2Cl_2 [b]	545 (2100),[c] 720 (s), 1560 (670)[c]	500 (s), 720 (1000)
1273-18-3	Fc(—C≡C—)$_2$Fc	CH_2Cl_2 [b]	510 (2220), 760 (670), 1180 (570)[c]	580 (s), 760 (1260)
59187-97-2	FDA	CH_2Cl_2 [b]	670 (960), 840 (s), 1760 (3100)	
1287-38-3	Biferrocene[d]	CH_3CN [e]	545 (2160), 680 (s), 1800 (750)	480 (920), 660 (1000)
11105-90-1	BFD[f]	CH_3CN	600 (370), 1550 (2100)	465 (2755)
1271-47-2	FcC≡CH	CH_2Cl_2 [b]	480 (s), 565 (300), 700 (310)	

[a] Reproducible within 5%. s = shoulder. [b] Containing n-Bu_4NBF_4 (0.1 M). [c] The experimentally determined ϵ has been corrected for % monocation in the equilibrium mixture (see electrochemistry discussion). [d] Reference 13. [e] Containing Et_4NClO_4 (0.1 M). [f] References 8 and 28.

than in I (about 3200 cm^{-1}), however, the oscillator strengths for the near-infrared transitions of all three are comparable. The interaction parameter can be estimated by eq 4

$$\alpha^2 \cong \frac{4.6 \times 10^{-9}\, \epsilon_{max} \Delta_{1/2}}{\bar{\nu} r^2} \qquad (4)$$

where ϵ_{max} is the molar absorptivity, $\Delta_{1/2}$ is the band width in cm^{-1}, $\bar{\nu}$ is the frequency in cm^{-1}, and r is the donor–acceptor distance. The interaction parameter, therefore, is largest in the biferrocene cation and decreases with greater donor–acceptor distance.[1]

Intuitively, we expect electronic and inductive effects to diminish as the distance between metal centers increases. For compounds I, III, and V, this is reflected in the cyclic voltammetric results. As the iron–iron distance increases, $\Delta E_{1/2}$, the separation in half-wave potentials, decreases. For this small series of mixed valence biferrocenes there appears to be a correlation between α and $\Delta E_{1/2}$.

The energy of the near-infrared band increases in going from the biferrocene cation (I) to the acetylene (III) to the butadiyne (V). Shifts to higher energy comparable to that of the butadiyne have been observed in the biferrocene series, but only for unsymmetrically substituted compounds.[30] According to the Hush model,[3] the energy (E_{op}) of the Frank–Condon transition for a one-electron transfer in a symmetrical compound is four times that needed to form a symmetrical transition state in the corresponding thermal exchange process (E_{th}). In principle, E_{th} can be calculated in terms of metal–ligand force constants and the difference in metal–ring bond lengths and stretching frequencies in the ferrocene and ferrocenium portions of the molecule. Within a series of biferrocenyl cations, the relative size of E_{th} (and the corresponding energy of the intervalence transfer band) gives a measure of the structural similarity between the ferrocene and ferrocenium halves of the mixed valence ion. In compounds I, III, and V, more reorganizational energy is required for electron transfer as the iron–iron distance increases.[31] From the data on the frequency and intensity of the near-infrared bands, it follows that less reorganizational energy is needed in the electron transfer process as the amount of delocalization in the ground state increases.

The opposite effect of frequency and intensity as a function of metal–metal distance is noted in the spectra of the mixed valence ferrocenophanes II and IV. The FDA ion has a near-infrared band at lower energy and higher intensity than the BFD ion. The ESR and electrochemical results suggest that FDA (2,3) may be a fully delocalized analogue of the BFD cation. If so, the results for neither ion can be interpreted in terms of the Hush model, for which a prerequisite of weak interaction prevails.

The similarity found in the ESR spectra of the FDA and BFD ions is corroborated by the qualitative features of their electronic spectra. Most conspicuous are the greater intensities of the near-infrared bands and lower intensities of the visible bands of the ferrocenophanes as compared to their singly fused derivatives. There is, however, one important difference. When the near-infrared spectrum of the BFD ion is plotted in the linear frequency representation, its resolution into two bands is apparent.[8] The combined bandwidth is roughly 4800 cm^{-1}. Two bands are not observed for the FDA ion in a similar representation. Owing to solvent absorption, however, extinction coefficients in the 1680–1780-nm region must be interpolated, and so the exact shape of the curve could not be determined. The band for FDA (2,3) is narrower; a bandwidth of 2800 cm^{-1} is estimated.

The 600-nm band of the ferrocenium ion has been assigned to the $^2E_{2g} \rightarrow {}^2E_{2u}$ ligand-to-metal transition.[26,27,32] This assignment was based, in part, on the effect of ring substituents on the energy of the band. Inductively, an acetylene group is electron withdrawing. This is reflected in the half-wave potential of ferrocenylacetylene (FcC≡CH) which is some 180 mV higher than that of ferrocene in methylene chloride. A corresponding increase in energy of the "ferrocenium" transition is expected for acetylene substituted ions.

The situation, however, is somewhat more complicated. At least three bands are observed in the visible spectrum of the ferrocenylacetylene cation. These bands may result from separate ligand to metal transitions from the substituted and unsubstituted cyclopentadienyl rings. A similar suggestion was made for substituted biferrocenyl cations.[13]

In the visible spectra of the mixed valence acetylenes III–V, at least two bands are observed. Since we expect weak iron–iron interactions in ions III and V, we assume that these bands are due to typical transitions of substituted ferrocenium ions as found for other substituted biferrocene monocations. The spectra of the dications of III and V show features similar to those of the biferrocene dication.[13]

If the FDA monocation is a fully delocalized system, we would not expect to see transitions due to either of the constituent halves. In the FDA ion (IV), as in the BFD ion, the visible transitions are of lower intensity and energy than those of the corresponding singly bridged cations.

Conclusions

It has previously been demonstrated[1] that the biferrocene cation is a class II mixed valence compound under the categories defined by Day.[4] On the basis of the electrochemical results and the visible and near-infrared absorption spectra, the singly bridged acetylene cations III and V also appear to be members of this class. The spectral data on the near-infrared bands can be interpreted in terms of the Hush model for intervalence transfer transitions.

It has also been shown[2] that BFD (2,3) has properties that are quite different from biferrocene (2,3), and ion II may, in fact, be a class III mixed valence compound. The electrochemistry, ESR, and electronic absorption spectra of FDA

(2,3) closely resemble those of BFD (2,3). Based on these observations, we conclude that the π-bridged FDA (2,3) ion is a fully delocalized analogue of BFD (2,3). The question remains as to why BFD (2,3) is a delocalized ion while biferrocene (2,3) is not. Two possible contributing factors in the case of BFD have been cited: the proximity of the iron atoms and the fused π-ligand system. This study shows the importance of the latter.

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References and Notes

(1) D. O. Cowan, C. LeVanda, J. Park, and F. Kaufman, *Acc. Chem. Res.*, **6**, 1 (1973).
(2) C. LeVanda, D. O. Cowan, K. Bechgaard, U. T. Mueller-Westerhoff, P. Eilbracht, G. A. Candela, and R. L. Collins, *J. Am. Chem. Soc.*, **98**, 3181 (1976).
(3) N. S. Hush, *Prog. Inorg. Chem.*, **8**, 391 (1967).
(4) M. B. Robin and P. Day, *Adv. Inorg. Chem. Radiochem.*, **10**, 247 (1967).
(5) The notation (2,3) is used for the mixed valence monocations. Similarly, (2,2) and (3,3) refer to the neutral molecule and dication, respectively.
(6) F. Kaufman and D. O. Cowan, *J. Am. Chem. Soc.*, **92**, 6198 (1970).
(7) D. O. Cowan and C. LeVanda, *J. Am. Chem. Soc.*, **94**, 9271 (1972).
(8) U. T. Mueller-Westerhoff and P. Eilbracht, *J. Am. Chem. Soc.*, **94**, 9272 (1972).
(9) D. O. Cowan, R. L. Collins, and F. Kaufman, *J. Phys. Chem.*, **75**, 2026 (1971).
(10) D. O. Cowan, J. Park, M. Barber, and P. Swift, *Chem. Commun.*, 1444 (1971).
(11) D. O. Cowan, G. A. Candela, and F. Kaufman, *J. Am. Chem. Soc.*, **93**, 3889 (1971).
(12) D. O. Cowan, C. LeVanda, R. L. Collins, G. A. Candela, U. T. Mueller-Westerhoff, and P. Eilbracht, *J. Chem. Soc., Chem. Commun.*, 329 (1973).
(13) C. LeVanda, D. O. Cowan, and K. Bechgaard, *J. Am. Chem. Soc.*, in press.
(14) C. LeVanda, D. O. Cowan, C. Leitch, and K. Bechgaard, *J. Am. Chem. Soc.*, **96**, 6788 (1974).
(15) M. Rosenblum, N. Brawn, J. Papenmeier, and M. Applebaum, *J. Organomet. Chem.*, **6**, 173 (1966).
(16) M. Rosenblum, N. M. Brawn, D. Ciappenelli, and J. Tancrede, *J. Organomet. Chem.*, **24**, 469 (1970).
(17) K. Schlogl and H. Egger, *Monatsh. Chem.*, **94**, 376 (1963).
(18) V. D. Parker, unpublished results.
(19) R. S. Nicholson and I. Shain, *Anal. Chem.*, **36**, 706 (1964).
(20) G. M. Brown, T. J. Meyer, D. O. Cowan, C. LeVanda, F. Kaufman, P. V. Roling, and M. D. Rausch, *Inorg. Chem.*, **14**, 507 (1975).
(21) J. E. Gorton, H. L. Lentzner, and W. E. Watts, *Tetrahedron*, **27**, 4353 (1971).
(22) (a) F. Ammar and J. M. Saveant, *J. Electroanal. Chem. Interfacial Electrochem.*, **47**, 215 (1973); (b) D. S. Polcyn and I. Shain, *Anal. Chem.*, **38**, 370 (1966).
(23) W. H. Morrison, Jr., S. Krogsrud, and D. N. Hendrickson, *Inorg. Chem.*, **12**, 1998 (1973).
(24) D. O. Cowan, P. Shu, and K. Bechgaard, unpublished results.
(25) R. Prins, *Mol. Phys.*, **19**, 603 (1970).
(26) R. Prins, *Chem. Commun.*, 280 (1970).
(27) Y. S. Sohn, D. N. Hendrickson, and H. B. Gray, *J. Am. Chem. Soc.*, **93**, 3603 (1971).
(28) U. T. Mueller-Westerhoff and P. Eilbracht, *Tetrahedron Lett.*, 1855 (1973).
(29) (a) B. Mayoh and P. Day, *Inorg. Chem.*, **13**, 2273 (1974); (b) B. Mayoh and P. Day, *J. Chem. Soc., Dalton Trans.*, 846 (1974).
(30) C. LeVanda, D. O. Cowan, K. Bechgaard, and M. D. Rausch, to be submitted for publication.
(31) Results in diruthenium ammine complexes show a similar dependence of band energy and intensity as a function of metal–metal distance: R. W. Callahan, G. M. Brown, and T. J. Meyer, *J. Am. Chem. Soc.*, **96**, 7829 (1974).
(32) In ref 14, an incorrect assignment was inadvertently written.

Halogen–Metal Exchange in Esters of Haloaryl Acids[1]

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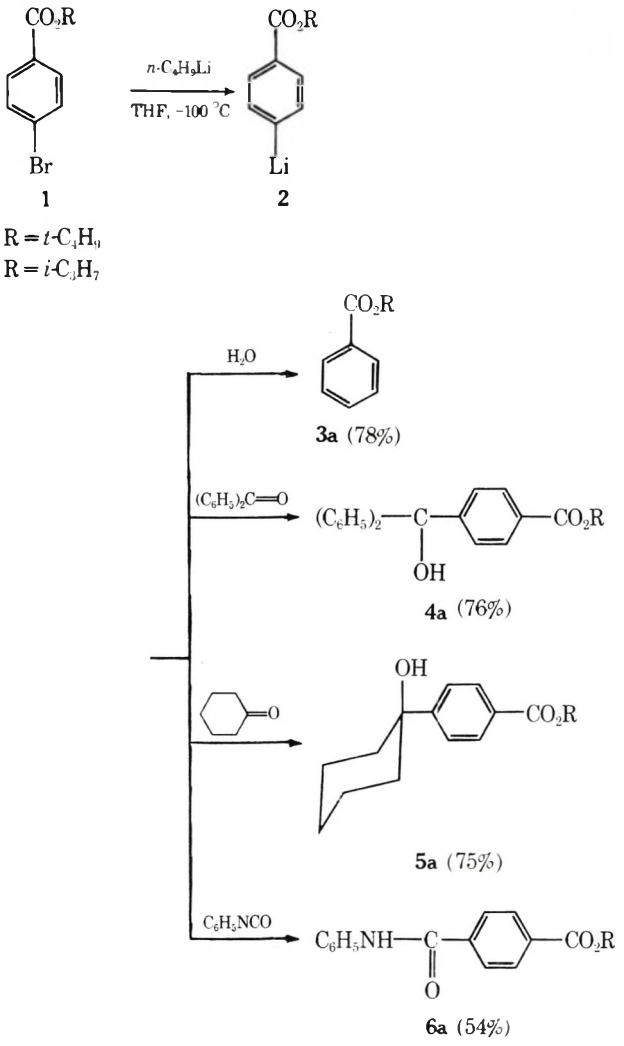
n-Butyllithium reacts selectively at −100 °C in THF–hexane with *tert*-butyl *p*-bromobenzoate by halogen–metal exchange; the resulting *tert*-butyl *p*-lithiobenzoate is stable at −100 °C and can be elaborated in high yield to give para-substituted *tert*-butylbenzoates by reactions with electrophiles. The less hindered isopropyl esters are not stable to aryllithium at −100 °C unless further hindered by ortho substitution.

Considerable progress has been made recently in developing improved procedures for the elaboration of aromatic acids utilizing derived aryllithium reagents. The method of Meyers[2] involving direct ortho metalation of oxazolines derived from aromatic acids would appear to be the method of choice for symmetrically substituted 2-aryloxazolines, since the ortho-substituted aryl halide corresponding to the position of lithiation is not a required intermediate as in halogen–metal exchange reactions. The alternative procedure,[3a] developed in our laboratory, involving direct halogen–metal exchange of the lithium salts of bromoarylcarboxylic acids at very low temperature (−100 °C) affords good yields of elaborated acids, subsequent to reaction with E^+. In addition, the process is positionally selective at the site occupied by bromine in the starting acid and is applicable to o-, *m*-, or *p*-bromobenzoic acids, as is the complementary procedure employing oxazolines to mask carboxyl functions to Grignard reagents.[4]

It has been shown that stable aryllithium reagents can be prepared at −100 °C with a variety of aryl bromides containing reactive functional groups (COO^-,[3] CN,[5] CH_2Cl,[6] CH_2CH_2Br,[6] *o*-NO_2[7]); however, similar reactions[8] with aryl halides containing methyl ester functions are of limited synthetic utility since the derived aryllithium reagents either self-condense or react with unchanged bromoaryl ester at low temperature (−78 → −100 °C) to give high yields of methyl benzoylbenzoates. In order to further define the limitations for synthetic reactions of aryllithium reagents containing ester functions, we have examined, as model compounds, halogen–metal exchange with *tert*-butyl *p*-bromobenzoate, isopropyl p-bromobenzoate, and isopropyl o-bromobenzoate. In all cases, progress of halogen–metal exchange was followed by quenching aliquots with water and determining (by NMR, GLC, and isolation of products) the ratio of starting bromoaryl ester to ester derived by replacing bromine with hydrogen.

While reaction of *tert*-butyl *p*-bromobenzoate (**1a**)[9] with *n*-propyllithium in ether at −40 °C is reported to involve preferential addition of alkyllithium to the ester function, the reaction of **1a** with *n*-butyllithium in THF–hexane at −100 °C involves selective halogen–metal exchange to give only **2a**. Reaction was complete after 5 min at −100 °C, and good yields (isolated) of elaborated aryl esters were obtained by reaction of **2a** with suitable electrophiles as shown in Scheme I.

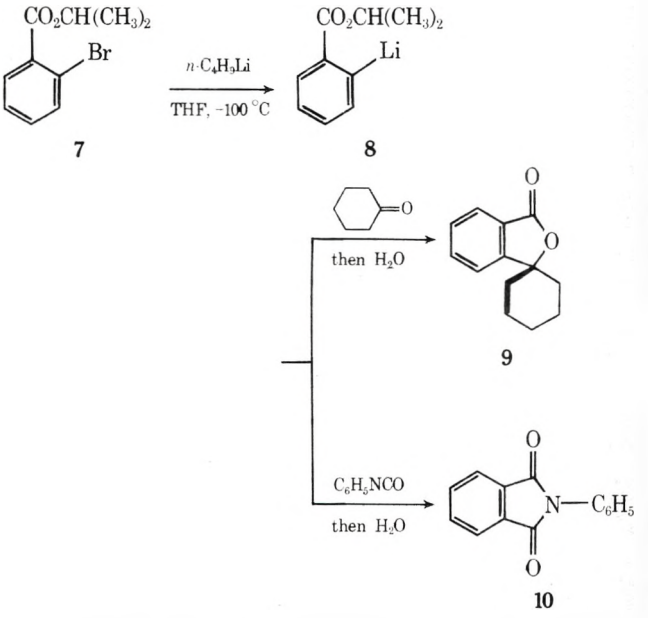
Scheme I



While **2a** is stable (during 2-h period examined) at −100 °C, some loss to condensation products was observed when the solution containing **2a** was warmed to −78 °C (1 h); extensive reaction occurred to give an unresolved multicomponent mixture (TLC) of presumably higher condensation products when the solution containing **2a** was warmed to −20 °C.

Reaction of the less hindered ester isopropyl *p*-bromobenzoate (**1b**), under similar conditions with *n*-butyllithium at −100 °C, was rapid (complete disappearance of **1b** after 5 min); however, a complex mixture of products resulted when the reaction mixture was quenched with water. Products identified were isopropyl benzoate (**3b**, 9% yield), isopropyl (*p*-bromobenzoyl)benzoate (~26% yield), and the carbinol corresponding to addition of *n*-butyllithium to isopropyl (*p*-bromobenzoyl)benzoate (~19% yield, slightly impure) together with considerable material (low R_f) assumed to be higher molecular weight condensation products. These products are analogous to, but more complex than, those reported[8] from the corresponding methyl ester of *p*-bromobenzoic acid.

The ester function in isopropyl o-bromobenzoate (**7**) is sufficiently hindered to permit complete halogen–metal interchange to give **8**. Studies of aliquots showed only isopropyl o-lithiobenzoate (**8**) after 5 min at −100 °C; the composition of aliquots taken over a 2-h period at −100 °C showed no appreciable change. When the solution containing **8** was quenched at −100 °C, shortly after its formation, with excess cyclohexanone, a mixture was obtained from which the expected lactone **9** was isolated in 43% yield; *N*-phenylphthalimide (**10**) was isolated in 53% yield when the reaction mixture



was quenched with excess phenyl isocyanate. These routes to **9** and **10** are inferior to those previously described from o-bromobenzoic acid[3a] or from o-bromobenzonitrile.[5] When the solution of **8** was warmed to −75 °C it decomposed to a complex unresolved mixture, a result in contrast to similar reactions[8] with methyl *o*-bromobenzoate which gave high yields (88%) of methyl *p*-benzoylbenzoate.

In summary, stable aryllithium reagents can be prepared and elaborated in good yields with electrophiles provided that the ester is derived from a tertiary alcohol or is otherwise sterically hindered. These procedures are not only useful for preparation of substituted benzoic esters and acids derived from them, but may offer advantages, in certain cases, to direct use of haloaryl acids, since the lithioaryl esters are generally more soluble at −100 °C than the corresponding lithioaryl carboxylates.[3e]

Experimental Section

Reaction of *tert*-Butyl *p*-Bromobenzoate (1a). General Procedure. 1-(*p*-Carbo-*tert*-butoxyphenyl)cyclohexanol (5a). *n*-Butyllithium (7.9 ml, 0.0195 mol, 2.45 M solution in hexane) was added, at a rate such that the temperature did not exceed −100 °C, to a cold (−100 °C, liquid nitrogen/diethyl ether bath) mixture of *tert*-butyl *p*-bromobenzoate [NMR ($CDCl_3$) δ1.56 (s, 9, CH_3), 7.45 (m, 3, ArH), 8.05 (m, 2, ArH)] (5.0 g, 0.0195 mol), tetrahydrofuran (130 ml, freshly distilled from $LiAlH_4$), and hexane (35 ml, stored over molecular sieves). The mixture was stirred for 5 min at −105 °C and cyclohexanone (2.45 g, 0.025 mol) was added at a rate such that the temperature was maintained at −98 °C. The resulting mixture was stirred for 5 min, allowed to warm to room temperature, and then poured into water (~100 ml). The aqueous layer was extracted with ether. The white solid (5.78 g, mp 91–108 °C) obtained from the dried ($MgSO_4$) ether extract was recrystallized from petroleum ether (bp 63–75 °C) to give 5.39 g (75% yield) of **5a** [mp 128–129 °C; NMR ($CDCl_3$) δ 1.60 (s, 9, CH_3), 1.45–2.00 (m, 11, aliphatic H and OH), 7.59 (d, 2, ArH), 7.98 (d, 2, ArH)].

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.97; H, 8.71.

Other compounds shown in Scheme I were prepared similarly.

***tert*-Butyl Benzoate (3a):** 78% yield; bp 44 °C (0.03 Torr); $n^{25}D$ 1.4886 (lit.[10] $n^{25}D$ 1.4896).

Triarylcarbinol 4a. From 0.02 mol of **1a** and 1 molar equiv of *n*-BuLi, benzophenone (0.025 mol) in dry THF (30 ml) was added at −100 °C. The crude product (9.20 g) was recrystallized from petroleum ether (bp 60–90 °C) to give a 76% yield of **4a** [mp 115–116 °C; NMR ($CDCl_3$) δ 1.60 (s, 9, CH_3), 3.25 (s, 1, OH), 7.30 (s, 10, ArH), 7.35 (d, 2, ArH), 7.92 (d, 2, ArH)].

Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 80.25; H, 6.48.

***p*-Carbo-*tert*-butoxy-*N*-phenylbenzamide (6a).** From 0.02 mol of **1a** and 1 molar equiv of *n*-BuLi, phenyl isocyanate (0.02 mol) in dry THF (~15 ml) was added at −95 °C. The crude solid (6.10 g, mp

121–131 °C) was recrystallized from a mixture (80/20) of petroleum ether (bp 90–110 °C) and chloroform to give a 54% yield of **6a** [mp 147–148 °C; NMR ($CDCl_3$) δ 1.60 (s, 9, CH_3), 7.50 (m, 5, ArH), 7.90 (m, 4, ArH), 8.45 (broad s, 1, NH)].

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.93; H, 6.52; N, 4.53.

Reactions of Isopropyl *p*-Bromobenzoate (1b). Reactions with isopropyl *p*-bromobenzoate [bp 80 °C (0.03 Torr), 86% yield from *p*-bromobenzoyl chloride and 2-propanol; composition analysis in agreement with $C_{10}H_{14}BrO_2$; NMR ($CDCl_3$) δ 1.45 (d, 6, CH_3), 5.40 (m, 1, CH), 7.50 (m, 3, ArH), 8.15 (m, 2, ArH)] were carried out as described for **1a**. Aliquots taken after 5 min showed considerable amounts of condensation products. The mixture was stirred for a total of 50 min at −105 °C and then poured into water. The organic product obtained from the dried ($MgSO_4$) ether extracts showed at least seven components by TLC. A portion (500 mg) of the product was purified by preparative TLC [silica gel, fluorescent indicator, petroleum ether (bp 30–60 °C) and ether mixture (90/10) as eluent] to give in order of decreasing R_f (1) isopropyl benzoate [9% yield; NMR ($CDCl_3$) δ 1.45 (d, 6, CH_3), 5.40 (m, 1, CH), 7.50 (m, 3, ArH), 8.15 (m, 2, ArH)]; (2) isopropyl *p*-bromobenzoylbenzoate [26% yield, mp 82–83 °C from petroleum ether (bp 60–90 °C); NMR ($CDCl_3$) δ 1.45 (d, 6, CH_3), 5.38 (m, 1, CH), 7.71 (s, 4, ArH), 7.85 (d, 2, ArH), 8.1 (d, 2, ArH) (Anal. Calcd for $C_{17}H_{15}BrO_3$: C, 58.81; H, 4.85; Br, 23.02. Found: C, 58.77; H, 4.42; Br, 23.16)]; (3) an oil, slightly impure alcohol corresponding to the product obtained by addition of *n*-butyllithium to isopropyl *p*-bromobenzoylbenzoate [19% yield; NMR ($CDCl_3$) δ 0.9 (t, 3, CH_3), 1.40 (d, ~6, CH_3), 1.40 (m, ~6, CH_2), 5.35 (m, 1, CH), 7.55 (m, 6, ArH), 8.10 (d, 2, ArH); ir (CCl_4) ν_{OH} 3440 cm^{-1}, $\nu_{C=O}$ 1710 cm^{-1}]; and (4) the major fraction, with low R_f, which was a complex mixture.

Reactions of Isopropyl *o*-Bromobenzoate (7). Isopropyl *o*-bromobenzoate [**7**, 83% yield from *o*-bromobenzoyl chloride and 2-propanol, bp 86–87 °C (0.01 Torr); NMR ($CDCl_3$) δ 1.38 (d, 6, CH_3), 5.13 (m, 1, CH), 7.43 (m, 4, ArH) (Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56; Br, 32.87. Found: C, 49.18; H, 4.58; Br, 32.76)] was treated with *n*-BuLi as described for **1a**. Studies (NMR) of aliquots taken after 5 min showed absence of starting bromo ester and only isopropyl benzoate.

Lactone 9. To the solution prepared from bromo ester **7** (0.0206 mol) and *n*-BuLi stirred for 20 min at −105 °C was added cyclohexanone (0.03 mol) in dry THF (~25 ml) at −100 °C. The resulting solution was allowed to warm to 10 °C and was poured into dilute hydrochloric acid (~100 ml). The acidic solution was extracted with ether and the organic material obtained from the dried ($MgSO_4$) ether extracts was saponified (1.5 h) with hot 90% ethanolic KOH. The solution was cooled and extracted with ether (the ether extract contained 1.39 g of an oil which was resaponified and reprocessed to give 0.34 g, 9% yield, of lactone **9**). The alkaline mixture was made acidic (pH ~2) with concentrated hydrochloric acid and warmed at 50 °C for 5 min. The cooled solution was extracted with ether, which was subsequently washed rapidly with cold 5% aqueous NaOH. Lactone **9** (1.35 g, 34% yield, total yield 43%, mp and mmp[5] 79–80 °C) was obtained from the dried ($MgSO_4$) ether extract by recrystallization of the crude product from petroleum ether (bp 30–60 °C).

***N*-Phenylphthalimide (10).** Phenyl isocyanate (0.05 mol) in dry THF (~25 ml) was added at −98 °C to the solution prepared from isopropyl *o*-bromobenzoate (0.020 mol) 5 min after the addition of *n*-BuLi. The mixture was allowed to warm to 25 °C and was poured into water (~100 ml). Phthalimide **10** (mp 208–210 °C, from ethanol/chloroform, mmp 206–209 °C, lit.[11] mp 208 °C) was obtained in 53% yield by recrystallization of the solid mixture obtained from the dried ($MgSO_4$) organic extracts. The concentrated mother liquor contained *N,N'*-diphenylurea (mp 237–242 °C dec, lit.[12] 239 °C, separated by trituration with petroleum ether in which the urea has limited solubility) and a product assumed to be slightly impure isopropyl *N*-phenylcarbamate [mp 85–86 °C, by preparative TLC with subsequent recrystallization from petroleum ether (bp 30–60 °C); lit.[13] mp 86 °C; NMR ($CDCl_3$) δ 1.30 (d, 6, CH_3), 5.05 (m, 1, CH), 6.6 (broad s, 1, NH), 7.20 (m, 5, ArH); ir (KBr) ν_{N-H} 3300 cm^{-1}, $\nu_{C=O}$ 1710 cm^{-1}].

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.82; N, 7.82. Found: C, 67.56; H, 7.24; N, 7.82.

Registry No.—**1a**, 59247-47-1; **1b**, 59247-48-2; **3a**, 774-65-2; **4a**, 59247-49-3; **5a**, 59247-50-6; **6a**, 59247-51-7; **7**, 59247-52-8; **9**, 5651-49-0; **10**, 520-03-6; *n*-butyllithium, 109-72-8; cyclohexanone, 108-94-1; benzophenone, 119-61-9; phenyl isocyanate, 103-71-9; *p*-bromobenzoyl chloride 586-75-4; 2-propanol, 67-63-0; isopropyl benzoate, 939-48-0; *o*-bromobenzoyl chloride, 7154-66-7; isopropyl *n*-phenylcarbamate, 122-42-9; isopropyl *p*-bromobenzoylbenzoate, 59247-53-9.

References and Notes

(1) Supported by Grant DAHCO4-74-GD128 by the U.S. Army Research Office.
(2) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 3158 (1975).
(3) (a) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **39**, 2051 (1974); (b) W. E. Parham, L. D. Jones, and Y. Sayed, *ibid.*, **40**, 2394 (1975).
(4) A. I. Meyers, D. L. Temple, D. Hardukewych, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2787 (1974).
(5) W. E. Parham and L. D. Jones, *J. Org. Chem.*, **41**, 1187 (1976).
(6) W. E. Parham, L. D. Jones, and Y. A. Sayed, *J. Org. Chem.*, **41**, 1184 (1976).
(7) G. Kobrich and P. Buck, *Chem. Ber.*, **103**, 1412 (1970).
(8) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **39**, 2053 (1974).
(9) B. F. Hofferth, *Iowa State Coll. J. Sci.*, **26**, 219 (1952).
(10) J. F. Norris and G. W. Rigby, *J. Am. Chem. Soc.*, **54**, 2088 (1932).
(11) M. P. H. van der Meulen, *Recl. Trav. Chim. Pays-Bas*, **15**, 287 (1896).
(12) G. Young and E. Clark, *J. Chem. Soc.*, **73**, 367 (1898).
(13) A. Michael and P. H. Cobb, *Justus Liebigs Ann. Chem.*, **363**, 84 (1908).

Metal–Ammonia Reduction. 15. Regioselectivity of Reduction and Reductive Methylation in the Fluorene Series[1]

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Reduction of fluorene with alkali metals in ammonia affords initially 2,4a-dihydro- and 1,4-dihydrofluorene (**2**, **3**) and not the 3,9a isomer previously reported. While **2** accords with molecular orbital prediction, **3** is only the second example of reduction contratheory. Analogous reductive methylation of fluorene with lithium and methyl bromide gave the 4a-methyl homologue of **2**, 4a-methyl-2,4a-dihydrofluorene, along with 9-methyl- and 9,9-dimethylfluorene. The products of similar reactions of 9,9-dimethylfluorene were principally the predicted 2,4a-dihydro derivatives accompanied by lesser amounts of the 1,4-dihydro isomers, namely 1,4-dihydro-9,9-dimethylfluorene and its 1-methyl homologue. Formation of the 2,4a-dihydro products is explicable in terms of the general mechanism previously proposed, while origin of the 1,4-dihydro compounds involves initial protonation unexpectedly at the 4 position. Formation of the 9-methylated derivatives of fluorene is ascribed to protonation by fluorene of the dianionic intermediate and methylation of the 9-fluorenyl anion.

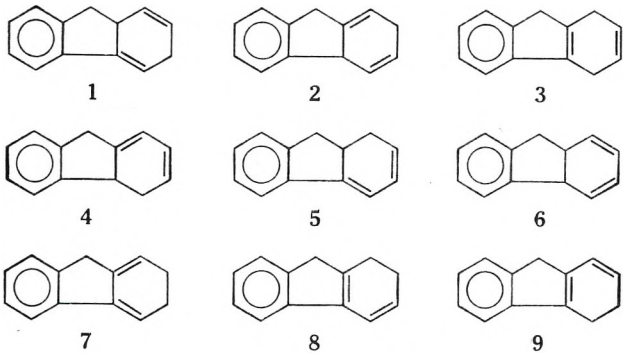
Reduction of polycyclic aromatic hydrocarbons by alkali metals in liquid ammonia has been shown in previous papers[1,3,4] to be controllable to the dihydro stage, to be regiospecific,[5] and to afford products in accord with predictions of

Table I. Reduction of Fluorene by Li and Ca in Ammonia[a]

Metal (mmolar equiv)	Temp, °C	Time, min	Product composition, % 2	3	Tetrahydro	Fluorene
Li (2.2)[b]	−78	5	39	37	8	11
Li (2.2)[b]	−33	5	29	35	10	26
Li (2.2)[c]	−78	5	43	30	4	20
Li (2.2)[c,d]	−33	30	27	46	1	25
Li (3.0)[b,e]	−78	10	31	27	0	36
Li (5.0)[b]	−33	20	38	2	51	2
Li (5.0)[b]	−33	30	27	3	62	1
Ca (2.2)[b]	−33	10	23	22	25	18

[a] Conditions are described in the Experimental Section. [b] The lithium metal was added last. [c] The lithium metal was dissolved before the addition of fluorene. [d] THF was employed in place of ether as cosolvent. [e] $FeCl_3$ (50 mg) was added before addition of fluorene.

Hückel molecular orbital (HMO) theory.[7] Several apparent discrepancies in the earlier literature were resolved upon reinvestigation.[1,3,6,8,9] Fluorene is the sole remaining hydrocarbon for which anomalous results have been reported. According to Hückel and Schwen,[10] fluorene upon treatment with sodium in liquid ammonia affords an unstable dihydrofluorene assigned the 3,9a-dihydro structure (**1**) on the basis of chemical evidence. On the other hand, HMO calculations[3,7] predict the 2,4a-dihydro structure (**2**) as the primary product;[11] **2** would also be expected by analogy with biphenyl from which 1,4-dihydrobiphenyl is the initial product.[3,8,12] Therefore, we undertook to reinvestigate this problem.

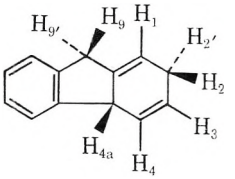


Results

Interaction of lithium metal with fluorene in liquid ammonia following the general technique developed earlier[1,8] furnished two dihydro derivatives (**2, 3**) along with tetrahydrofluorene and recovered fluorene. Product ratios were determined by GLC analysis and found to be markedly dependent upon reaction conditions (Table I). Reaction for 5 min at −78 °C quenched with NH_4Cl and worked up rapidly by extraction with ether afforded **2** (39%) and **3** (37%) accompanied by tetrahydrofluorene (8%) and fluorene (11%).

The structural assignments of the dihydro isomers, which were trapped off the GLC column, are based on the following considerations. The integrated NMR spectrum of the isomer assigned the 1,4-dihydro structure **3** exhibited a sharp allylic singlet at δ 3.05 (4 H), a benzylic singlet at 3.20 (2 H), an AB quartet (J = 9 Hz) in the vinyl region at 5.84 (2 H), and an aromatic multiplet at 6.96–7.33 (4 H) consistent with this relatively symmetrical structure. Structures **1** and **2** and the alternative structures **4**, **5**, and **6** may be ruled out immediately, since the integrated proton ratios are inconsistent with these assignments. The ultraviolet spectrum of **3** had λ_{max} 259 nm (ε 11 000) compatible with the indene chromophore present in this ring system.[13] Further reduction of **3** with lithium in ammonia took place smoothly to afford a tetrahydrofluorene derivative, the NMR spectrum of which still displayed two vinylic protons. This behavior is in accord with previous experience[1,3] that conjugated styrene-type double bonds undergo facile reduction, while isolated double bonds are resistant to further transformation with alkali metals in ammonia. The alternative 2,3-dihydrofluorene structure **7** may be rejected on several grounds. The observed chemical shift of the allylic protons (δ 3.05) occurs at unexpectedly low field for **7** and is more compatible with the doubly allylic protons of **3**. Also, the AB quartet pattern (J = 9 Hz) of the vinylic protons is unexpected for **7**. Moreover, reduction of **7**, presuming that it could be limited to the tetrahydro stage, should furnish a tetrahydrofluorene with at most one vinyl hydrogen atom.[15] Therefore, structure **7** may be rejected. The two additional structures **8** and **9** can also be ruled out since the observed chemical shift (δ 3.05) of the allylic protons is much more consistent with the doubly allylic assignment of **3**. The ultraviolet spectral data are also incompatible with **8** or **9**, since the maximum absorption of these more conjugated chromophores is anticipated to occur at considerably longer wavelength than observed.[17]

The 2,4a-dihydro structure **2** was assigned the second dihydro isomer on the basis of the integrated ^1H NMR spectrum. The benzylic proton at H_{4a}, uniquely characteristic of this structure, appeared as a multiplet at δ 3.69, while the two additional benzylic protons at H_9 were found as an AB quartet at δ 3.50 (J = 18 Hz). An analysis of the vinyl region showed an apparent singlet at δ 5.58, a multiplet at 5.86, and a doublet at 6.09 assigned to H_1, H_3, and H_4, respectively. The downfield signal assigned at H_4 was part of a basic AB pattern ($J_{3,4}$ = 9.7 Hz) which exhibited additional coupling to the allylic proton(s) δ 2.72 (J = 2.6 Hz). Irradiation of the allylic protons at δ 2.72 simplified the signal at 5.86 to a doublet of doublets ($J_{3,4}$ = 9.7 and $J_{3,4a}$ = 3.3 Hz). This general pattern is consistent with that observed for analogous 1,4-dihydroaromatic molecules,[1] and for the 4a-methyl homologue of **2** discussed in following paragraphs.



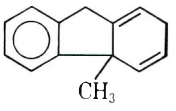
Analogous reductive methylation of fluorene with lithium in liquid ammonia followed by methyl bromide gave the 4a-methyl homologue of **2**, 4a-methyl-2,4a-dihydrofluorene (**10**), along with 9-methylfluorene and 9,9-dimethylfluorene, the relative proportions of which proved dependent upon reaction conditions (Table II).

The NMR spectrum of **10** closely resembled that of **2**, exhibiting a pair of allylic protons as a multiplet at δ 2.65, an AB quartet (J = 19 Hz, δ_A 3.73, δ_B 3.28) assigned to the benzylic

Table II. Reductive Methylation of Fluorene with Lithium and Methyl Bromide in Liquid Ammonia[a]

Time, min	Temp, °C		Product composition, % 9-Methyl-fluorene	9,9-Dimethyl-fluorene	Fluorene
		10			
5[b]	−78	38	37	5	12
5[c]	−78	45	26	13	4
10[b]	−78	33	36	21	1
30[b]	−33	40	0	30	1

[a] Conditions are described in the Experimental Section. [b] Lithium metal was added last. [c] Lithium metal was dissolved before addition of fluorene.

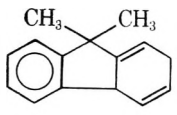


10

protons, three vinylic protons as multiplets at 5.52 (H_1) and 5.70 (H_3) and a doublet of doublets at 6.14 (H_4), and an aromatic multiplet (4 H) at 6.95–7.18. On decoupling by irradiation at δ 2.65, the H_3 and H_4 signals sharpened to clear doublets (J = 10.5 Hz for each) and the H_1 multiplet collapsed to a sharp singlet. The ultraviolet spectrum showed λ_{max} 256 nm (ϵ 2650), confirming the lack of conjugation with the aromatic ring.[18]

The origin of the side products, 9-methylfluorene and 9,9-dimethylfluorene, which accompany **10** is not immediately evident. Their formation, however, is indicative of involvement of the relatively acidic benzylic protons of fluorene in the foregoing reactions. It was of interest, therefore, to investigate the analogous transformations of 9,9-dimethylfluorene. Reduction of the latter with lithium in ammonia under conditions similar to those employed with fluorene afforded the anticipated analogue of **2**, i.e., 9,9-dimethyl-2,4a-dihydrofluorene (**11**), along with a second dihydro isomer characterized as 9,9-dimethyl-1,4-dihydrofluorene (**12**). Compound **11**, like the related dihydrofluorene isomer **2**, proved relatively unstable, undergoing spontaneous reversion to the parent hydrocarbon. The failure of Huckel and Schwen[10] to detect appreciable reaction between sodium and 9,9-dimethylfluorene in liquid ammonia is probably a consequence of decomposition of the dihydro products to 9,9-dimethylfluorene during the more prolonged and drastic workup procedure employed by these authors. Owing to its instability, **11** could not be obtained entirely free of **12** and 9,9-dimethylfluorene. The structural assignment, therefore, is based upon its NMR spectrum in the mixture, which closely resembled that of **2** and **10**, and upon characterization of its 4a-methyl analogue obtained as the major product of analogous reductive methylation.

Assignment of the structure of **12** is based on the NMR and



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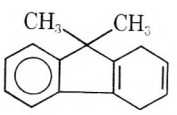

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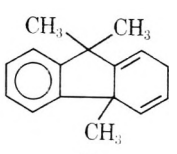

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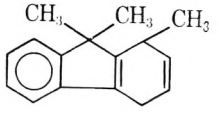

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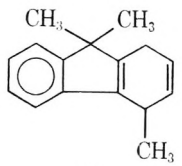


15

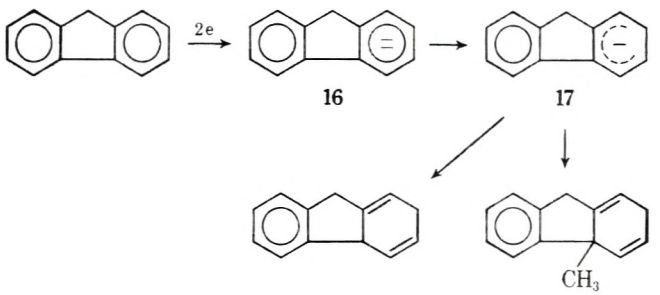
uv spectral data and upon characterization of the analogous product of reductive methylation of 9,9-dimethylfluorene as 1,9,9-trimethylfluorene (**14**). The uv spectrum of **12** had λ_{max} 262 nm (ϵ 12 200), which is consistent with **3** (λ_{max} 259 nm, ϵ 11 000)[13] and inconsistent with the alternative structures[17] analogous to **4–9**, which are thereby eliminated from consideration. The integrated NMR spectrum of **12** exhibited methyl, allylic, vinylic, and aromatic protons in the ratio of 6:4:2:4. The alternative 3,9a-dihydro structures analogous to **1**, as well as the 4,4a-, 1,9a-, and 4a,9a-dihydro structures analogous to **4**, **5**, and **6**, are expected to exhibit different patterns, and may therefore be rejected. Thus, **12** remains as the only structure consistent with the data.

Reductive methylation of 9,9-dimethylfluorene was carried out in order to trap the unstable **11** in the form of its 4a-methyl derivative. As anticipated, the major product (50–80% yield) was 4a,9,9-trimethyl-2,4-dihydrofluorene (**13**). It was accompanied by a second new compound identified as **14.** In confirmation of the structure of **13**, the integrated NMR spectrum exhibited the pattern seen for other 2,4a-dihydrofluorene derivatives, displaying methyl singlets at δ 1.28, 1.39, and 1.43 (9 H), an allylic multiplet centered at 2.72 (2 H), vinyl protons (2 H) as a multiplet at 5.63–5.97 (H_1 and H_3) and as a doublet (J = 9.5 Hz) at 6.26 (H_4), and an aromatic multiplet (4 H). The ultraviolet spectrum showed λ_{max} 271 nm (ϵ 2000), confirming the lack of conjugation between the olefinic groups and the aromatic ring.[13] Compound **14**, identified as 1,9,9-trimethyl-1,4-dihydrofluorene, exhibited an NMR spectral pattern resembling that of **12**, the minor product of reduction of 9,9-dimethylfluorene. To establish with greater certainty the position of attachment of the third methyl group in **14**, the latter was dehydrogenated with o-chloranil. The resulting trimethylfluorene (mass spectrum m/e 208) was a colorless oil which exhibited methyl peaks at δ 1.55 (6 H) and 2.50 (3 H) in the NMR spectrum. It was identified as 1,9,9-trimethylfluorene by comparison with an authentic sample synthesized from 1-methylfluorene through reaction with n-butyllithium and methyl bromide. The NMR spectra and retention times on GLC and TLC of both samples were identical. Since the alternative 4,9,9-trimethyl-1,4-dihydrofluorene structure (**15**) was also compatible with the uv and NMR spectral data for **14**, it was necessary to synthesize also 4,9,9-trimethylfluorene. This was accomplished through oxidative rearrangement of **13** with trityl fluoroborate according to the method described previously.[19] The NMR spectrum of 4,9,9-trimethylfluorene differed from that of the 1,9,9 isomer in several respects, notably the chemical shifts of the methyl singlets which appeared at δ 1.43 (6 H) and 2.65 (3 H). The retention times on GLC were also different. Therefore, **15** can be excluded as the structure of the second trimethyldihydrofluorene isomer, which is thereby established unequivocally as **14.**

Discussion

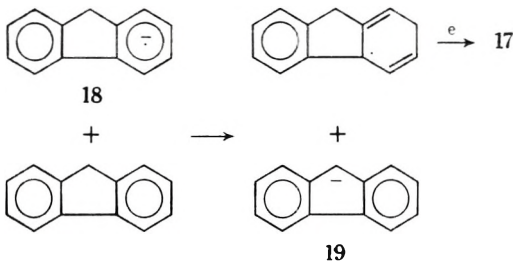
The principal products of both reduction and reductive methylation of fluorene and 9,9-dimethylfluorene are the 2,4a-dihydrofluorene derivatives (i.e., **2**, **10**, **11**, **13**). This is in accord with HMO theoretical prediction and contrary to the claim of Huckel and Schwen.[10] The mechanism of these transformations, based on the detailed study of the analogous transformations of the closely related biphenyl ring system,[8] can be presumed to involve (1) rapid addition of two electrons to form the fluorenyl dianion (**16**); (2) fast protonation by the medium in the 2 position, the site of maximum electron density; and (3) survival of the resulting monoanion (**17**) sufficiently long to undergo either kinetic protonation by a more acidic proton source (e.g., NH_4Cl) or alkylation with methyl bromide at the benzylic position.

The origin of the minor products is of considerable interest,

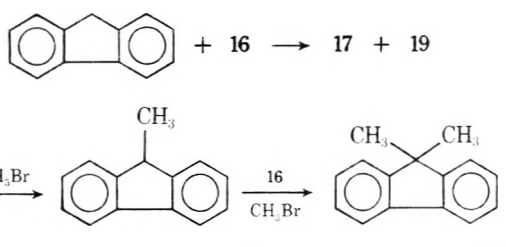


since reduction partially contrary to HMO theoretical prediction is clearly documented for only *p*-terphenyl.[6] In the present case, the principal minor products of reduction and reductive methylation are the respective 1,4-dihydrofluorene derivatives **3**, **12**, and **14**. Evidently, initial protonation takes place at either the 1 or the 4 positions. Characterization of the minor product of reductive methylation of 9,9-dimethylfluorene as the 1-methyl derivative, **14**, indicates that protonation in the 4 position is preferred in this case. It would be unsafe, however, to generalize on the basis of this single example. In the case of *p*-terphenyl it was shown that protonation contrary to prediction was a consequence of ion pair association, and by appropriate variation of the cation, solvent, and other parameters the site of proton addition could be controlled.[6] In the present case, attempts to demonstrate similar effects (Table I) gave inconclusive results.

An unusual feature of fluorene with respect to hydrocarbons previously investigated is the relative acidity of the benzylic protons (pK_a 25).[20] Reaction of fluorene with lithium metal in THF has been shown to afford 9-lithiofluorene (**19**) and a mixture of tetra- and hexahydrofluorenes.[16] The mechanism proposed involves protonation by fluorene of the radical anion **18** produced on interaction of lithium and fluorene, followed by addition of a second electron from unreacted lithium to the resulting radical to form the anion **17** capable of metalating another molecule of fluorene. In liquid ammonia with excess



lithium present a similar mechanism is unlikely, since the radical anion would be expected to undergo facile transformation to the dianion.[8] However, protonation of the dianion directly by fluorene to furnish the monoanions **17** and **19** is quite reasonable, since the relative acidity of fluorene (pK_a = 25)[20] exceeds that of ammonia (pK_a = 34).[20] Methylation of **19** leads to 9-methylfluorene, which in turn can undergo further reaction on the remaining benzylic hydrogen in similar



manner to provide 9,9-dimethylfluorene. This mechanism accounts most satisfactorily for the relatively large proportions of the methylfluorenes formed in reductive methylation (Table II).

The observed facility of 1,4-dihydrofluorene to undergo further reduction to tetrahydrofluorene deserves comment, since overreduction is not generally a serious complication when the standard procedures developed earlier in our laboratory[1,6,8] are employed. These procedures take advantage of the stability and resistance to further electron addition of many hydrocarbon anions in liquid ammonia by withholding addition of the protonating agent until the end of the reaction period, then adding a relatively acidic proton source (usually NH_4Cl) rapidly to quench reaction. The diminished effectiveness of this technique in this case suggests that the monoanion of 1,4-dihydrofluorene must itself be protonated already to some extent by the medium. The styrene-type double bond of the neutral hydrocarbon should, of course, undergo facile further reduction.

Experimental Section

Physical Data. ^1H NMR spectra were obtained on Varian T-60 and Bruker HX 270 spectrometers. Chemical shifts are reported relative to Me_4Si in CCl_4 unless specified otherwise; integration was consistent with all assignments. Microanalyses for C and H correct to ±0.3 were obtained for all new compounds and were submitted for review, except the dihydrofluorene derivatives **2** and **11**, which were too unstable to provide meaningful microanalytical data. GLC analyses were performed on a F & M Model 500 chromatograph employing a 6 ft × 0.25 in. 20% DEGS column on 60–80 mesh Chromosorb W at 125 and 135 °C with 20 psi helium pressure and 50 ml/min flow rate. Mass spectra were determined on a Finnigan 1015 mass spectrometer at 70 eV. Ultraviolet spectra were taken on a Cary Model 14 spectrometer.

Reactions in Liquid Ammonia. All reactions were conducted under helium (to avoid formation of lithium nitride) in a three-neck Morton flask fitted with a Dewar condenser. Precautions described in preceding papers[6,8] for the exclusion of impurities (moisture, air, peroxides in solvents, and metallic salts in ammonia) known to often have a deleterious effect on reactions in ammonia were scrupulously observed. Fluorene was recrystallized from methanol and dried in vacuo. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ before use. Ammonia was distilled into the reaction vessel through a column of barium oxide (10–20 mesh). Lithium wire (Lithco) was freshly cut and washed free of oil with hexane before use. Methyl bromide was purified by passage of the gas through a tube of silica gel and sand into the reaction vessel. Products were isolated rapidly by partition between ether and water to minimize isomerization and other secondary processes. NMR spectra were taken immediately upon isolation of products and before GLC or other procedures in order to detect any decomposition occurring during these processes.

9-Methylfluorene. *n*-Butyllithium (15% in hexane) (105 mmol) was added to a solution of fluorene (16.6 g, 100 mmol) in THF (300 ml) at −40 °C over a period of 10 min. The resulting orange solution was stirred at −40 °C for 80 min, then decolorized by a stream of gaseous methyl bromide bubbled into the solution (flow rate 60 mmol/min) over a period of 2 min. Then NH_4Cl (50 g in 300 ml of water) was added, followed by ether (200 ml), and products were isolated by conventional procedure. Recrystallization of the product from methanol afforded 9-methylfluorene (17.65 g, 98%) as colorless needles: mp 45–46 °C (lit.[21] 45–46 °C); NMR δ 1.50 (d, 3, CH_3), 3.85 (q, 1, H_9), and 7.73–7.06 ppm (m, 8, aromatic).

9,9-Dimethylfluorene. Reaction of 9-methylfluorene (7.98 g, 44 mmol) with *n*-butyllithium and methyl bromide following essentially the same procedure employed for monomethylation furnished 9,9-dimethylfluorene (8.44 g, 98%) as colorless needles: mp 96–97 °C (lit.[21,22] 95–96 °C); NMR δ 1.45 (s, 6, CH_3) and 7.67–7.05 ppm (m, 8, aromatic); uv (CH_3OH) λ 258 nm (ε 15 900) 262 (16 900), 265 (16 400), 272 (12 900), 289 (6600), 294 (5050), and 300 (11 000).

Reduction of Fluorene. A solution of fluorene (830 mg, 5 mmol) in ether (75 ml) was added to 150 ml of liquid ammonia in a dry ice bath at −78 °C followed by lithium wire (76 mg, 11 mmol), and 5 min later the deep brown solution was quenched by addition of solid NH_4Cl (20 g). Addition of water and ether followed by the workup procedure recommended above gave a solid product (820 mg) consisting of **2** (39%), **3** (37%), tetrahydrofluorene (8%), and recovered fluorene (11%) by NMR and GLC analysis; GLC retention times at 135 °C were 4.2, 6.4, 2.2, and 8.4 min, respectively. The relative yields of the product components were highly dependent upon reaction conditions (cf. Table I).

Samples of **2** and **3** were trapped off the GLC column. Compound **2** had NMR δ 2.72 (m, 2, allylic), 3.50 (AB quartet, 2, J = 18 Hz, δ_9

3.59, δ_9 3.41, $H_{9',9}$), 3.69 (m, 1, H_{4a}), 5.58 (apparent s, 1, H_1), 5.86 (m, 1, H_3) (decoupling the allylic protons at δ 2.72 simplified the signal at 5.86 to a doublet of doublets, $J_{3,4}$ = 9.7, $J_{3,4a}$ = 3.3 Hz), 6.09 (d of d, 1, $J_{3,4}$ = 9.7, $J_{4,4a}$ = 2.6 Hz, H_4), and 6.95–7.28 ppm (m, 4, aromatic); mass spectrum *m/e* 168 (parent ion). Compound **3** had mp 110–111 °C; NMR δ 3.04 (s, 4, allylic), 3.20 (s, 2, benzylic), 5.84 (AB quartet, 2, J = 9.0 Hz, δ_A 5.88 δ_B 5.78, vinylic), and 6.96–7.33 ppm (m, 4, aromatic); uv λ_{max} (CH_3OH) 259 nm (ϵ 11 000).

Reductive Methylation of Fluorene. Reaction was conducted as described for reduction except that prior to quenching with ammonium chloride a stream of gaseous methyl bromide was passed into the reaction vessel for 1 min to decolorize the solution (flow rate 60 mmol/min). GLC analysis of the product (871 mg) gave 4a-methyl-2,4a-dihydrofluorene (**10**), 9,9-dimethylfluorene, 9-methylfluorene, and recovered fluorene, having retention times at 135 °C of 3.0, 5.0, 7.2, and 8.4 min, respectively. The yields of each of these components were dependent upon reaction conditions (Table II).

Compound **10** trapped off the GLC column was a colorless liquid: NMR δ 1.18 (s, 3, CH_3), 2.65 (m, 2, allylic), 3.51 (AB quartet, 2, J = 19 Hz, δ_A 3.73, δ_B 3.28, H_9), 5.52 (m, 1, H_1), 5.70 (m, 1, H_3), 6.14 (d of d, 1, H_4), and 6.95–7.18 ppm (m, 4, aromatic); when the allylic protons were decoupled the H_3 and H_4 signals became doublets (J = 10.5 Hz) and the H_1 multiplet collapsed to a sharp singlet; uv (CH_3OH) λ 249 nm (ϵ 2390), 256 (2650, 262 (2450), 278 (550), and 291 (380).

Reduction of 9,9-Dimethylfluorene. Reaction of 9,9-dimethylfluorene (970 mg, 5 mmol) with lithium (76 mg, 11 mmol) in ammonia following the procedure described for similar reaction of fluorene afforded a product (950 mg) shown by GLC to contain **11** (38%), **12** (24%), and recovered dimethylfluorene (31%); GLC retention times at 125 °C were 4.4, 5.2, and 6.8 min, respectively. Samples of both **11** and **12** were trapped off the GLC column. The instability of **11** with respect to decomposition back to 9,9-dimethylfluorene prevented detailed analysis of its NMR spectrum which in the mixture resembled closely that of **2** and **10**. Compound **12** was an oil: NMR δ 1.21 (s, 6, CH_3), 2.85 (t, 2, J = 8.25 Hz, $H_{1',1}$), 3.06 (t, 2, J = 8.25 Hz, $H_{2',2}$), 5.87 (s, 2, vinylic), and 7.00–7.39 ppm (m, 4, aromatic); uv (CH_3OH) λ 262 nm (ϵ 12 200), 272 (9300), 282 (3370), 288 (2230), and 299 (2380).

Analogous reaction in THF with 2.5 equiv of lithium at −33 °C for 30 min gave **11** (60%), **12** (25%), and recovered dimethylfluorene (4%).

Reductive Methylation of 9,9-Dimethylfluorene. Reaction of 9,9-dimethylfluorene (970 mg, 5 mmol) with lithium and methyl bromide in ammonia according to the procedure employed with fluorene gave a product (985) mg) shown by GLC to consist of **13** (49%), **14** (12%), **11** (2%), and recovered 9,9-dimethylfluorene (33%); GLC retention times were 3.2, 5.5, 4.4, and 6.8 min, respectively. Distillation through a spinning band column furnished pure **13** as a colorless oil: bp 117 °C (10 mm); NMR δ 1.28 (s, 3, 4a-CH_3), 1.39 (s, 3, 9-CH_3), 1.43 (s, 3, 9-CH_3), 2.62–2.83 (m, 2, allylic), 5.63–5.97 (m, 2, $H_{1,3}$), 6.26 (d, 1, J = 9.5 Hz, H_4), and 7.08–7.27 ppm (m, 4, aromatic); uv (CH_3OH) λ 259 nm (ϵ 316), 264 (630), 271 (2000), and 289 (466). Compound **14** trapped off the GLC column was an oil: NMR δ 1.30 (d, 3, J = 6 Hz, 4-CH_3), 1.28 (s, 3, 9-CH_3), 1.42 (s, 3, 9-CH_3), 3.12 (m, 2, $H_{1',1}$), 3.28 (m, 1, H_2), 5.79 (AB quartet, 2, J = 12 Hz, δ_A 5.84, δ_B 5.74, $H_{3,4}$), and 7.03–7.36 ppm (m, 4, aromatic); uv (CH_3OH) λ 266 nm (ϵ 10 955) and 293 (1365).

Similar reaction in which 2.5 equiv of lithium, THF, −33 °C, and 2.5 h were employed afforded **13** (80%), **14** (9%), and recovered 9,9-dimethylfluorene (9%).

1,9,9-Trimethylfluorene. Reaction of 1-methylfluorene (720 mg, 4 mmol) with a sixfold excess of *n*-butyllithium and methyl bromide following essentially the same procedure employed for the preparation of 9,9-dimethylfluorene furnished 1,9,9-trimethylfluorene (817 mg, 3.93 mmol, 98%) as a colorless oil: NMR δ 1.55 (s, 6, 9-CH_3), 2.50 (s, 3, 1-CH_3), and 6.80–7.70 ppm (m, 7, aromatic); it showed one spot on TLC on silica gel and a single sharp peak on GLC.

Dehydrogenation of 1,9,9-Trimethyl-1,4-dihydrofluorene (14). A solution of **14** (17 mg) and *o*-chloranil (30 mg) in benzene (4 ml) was refluxed for 1 h. After cooling to room temperature, the residue was chromatographed on Florisil eluted with hexane to afford 1,9,9-trimethylfluorene as a colorless oil, mass spectrum (70 eV) *m/e* 208. Its NMR spectrum and retention times on TLC and GLC were identical with those of the authentic compound.

Dehydrogenation of 4a,9,9-Trimethyl-2,4a-dihydrofluorene (13). A solution of **13** (120 mg) and trityl fluoroborate (220 mg) in acetic acid (6 ml) was heated at refluxed for 1 h. Conventional workup furnished an oil (157 mg), NMR and GLC analysis of which indicated quantitative conversion to triphenylmethane and 4,9,9-trimethylfluorene. The latter was extracted from the mixture by its greater solubility in benzene. Pure 4,9,9-trimethylfluorene trapped off the GLC column was a colorless oil: NMR δ 1.43 (s, 6, 9-CH_3), 2.65 (s, 3, 4-CH_3), and 6.90–7.90 ppm (m, 7, aromatic); mass spectrum (70 eV) *m/e* 208.

Acknowledgment. Support of this research by the U.S. Public Health Service Research Grants CA-11968 and CA-05246 from the National Cancer Institute and by the Louis Block Fund of the University of Chicago is gratefully acknowledged. The HX-270 Brucker superconducting NMR spectrometer was provided through the University of Chicago Cancer Research Center Grant CA 14599.

Registry No.—**2,** 59247-36-8; **3,** 55297-18-2; **10,** 59247-37-9; **12,** 59247-38-0; **13,** 59247-39-1; **14,** 59247-40-4; methyl bromide, 74-83-9; fluorene, 86-73-7; 9-methylfluorene, 2523-37-7; 9,9-dimethylfluorene, 4569-45-3; 1-methylfluorene, 1730-37-6; 1,9,9-trimethylfluorene, 59247-41-5; 4,9,9-trimethylfluorene, 59247-42-6; lithium, 7439-93-2; calcium, 7440-70-2; ammonia, 7664-41-7.

References and Notes

(1) Part 14: R. G. Harvey, D. F. Lindow, and P. W. Rabideau, *Tetrahedron,* **28,** 2909 (1972).
(2) (a) University of Chicago; (b) Indiana-Purdue University.
(3) Reviews: R. G. Harvey, *Synthesis,* 161 (1970); A. J. Birch and G. Subba Rao, *Adv. Org. Chem.,* **8,** 1 (1972).
(4) P. P. Fu, R. G. Harvey, J. W. Pascal, and P. W. Rabideau, *J. Am. Chem. Soc.,* **97,** 1145 (1975).
(5) The only exception encountered to date is *p*-terphenyl, shown to afford 1′,4′-dihydro- and 1,4-dihydro-*p*-terphenyl in variable ratio dependent upon experimental conditions.[6]
(6) R. G. Harvey, D. F. Lindow, and P. W. Rabideau, *J. Am. Chem. Soc.,* **94,** 5412 (1972).
(7) A. Streitwieser, Jr., and S. Suzuki, *Tetrahedron,* **16,** 153 (1961); A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists", Wiley, New York, N.Y., 1961, p 425.
(8) D. F. Lindow, C. N. Cortez, and R. G. Harvey, *J. Am. Chem. Soc.,* **94,** 5406 (1972).
(9) R. G. Harvey and P. W. Rabideau, *Tetrahedron Lett.,* 3695 (1970).
(10) W. Hückel and R. Schwen, *Chem. Ber.,* **89,** 481 (1956).
(11) It is important to distinguish the primary product of reduction, which is seldom the most thermodynamically stable isomer, from products which may form secondarily through isomerization, disproportionation, and other processes which can occur prior to isolation. These secondary processes can be eliminated or greatly diminished by the rational experimental procedures (e.g., short reaction times, rapid quenching of reaction and isolation of products, etc.) developed in previous studies.[1,6,8]
(12) P. J. Grisdale, T. H. Regan, J. C. Doty, J. Figueras, and J. L. Williams, *J. Org. Chem.,* **33,** 1116 (1968).
(13) The closely related compound 1-phenyl-1,4-cyclohexadiene is reported to show λ_{max} 249 nm (ϵ 9300),[12] while indene exhibits λ_{max} 249 nm (ϵ 11 000).[14]
(14) R. A. Morton and A. J. A. DeGouveia, *J. Chem. Soc.,* 916 (1934).
(15) 1,2-Reduction would be expected to afford principally the unconjugated 2,3,4,4a-tetrahydrofluorene, while 1,4 addition of hydrogen should furnish the 1,2,3,4-tetrahydro isomer anticipated to undergo facile further transformation to hexahydrofluorene. The latter is a principal product of Birch reduction of fluorene with lithium and alcohol in THF.[16]
(16) J. J. Eisch and W. C. Kaska, *J. Org. Chem.,* **27,** 3745 (1962).
(17) The related 2-phenyl- and 1-phenyl-1,3-cyclohexadienes exhibit λ_{max} 276 nm (ϵ 8140) and 303 (ϵ 13 800), respectively[12].
(18) The related 3-phenyl-1,4-cyclohexadiene is reported to show λ_{max} 262 nm (ϵ 465).[12]
(19) D. F. Lindow and R. G. Harvey, *J. Am. Chem. Soc.,* **93,** 3786 (1971).
(20) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists", Wiley, New York, N.Y., 1961.
(21) G. W. H. Scherf and R. K. Brown, *Can. J. Chem.,* **38,** 697 (1960).
(22) P. M. G. Bavin, *Can. J. Chem.,* **38,** 882 (1960).

Electrochemical and Metal–Ammonia Reduction of 1,4-Dihalonorbornanes[1]

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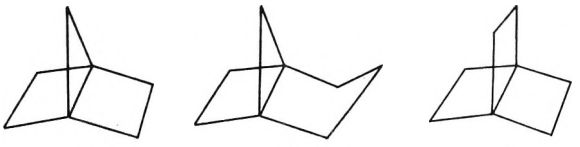
The electrochemical and metal–ammonia reductions of 1,4-dihalonorbornanes were examined as possible routes to the [2.2.1]propellane. The products were norbornane and 1,1′-binorbornane. In the metal–ammonia reductions, the amount of coupling product was found to be dependent on the concentration of the dihalide. It is suggested that local regions having a higher concentration of the dihalide may be responsible for the coupling.

The [2.2.1]propellane (**1**) is of particular interest in connection with the difference in thermal reactivity between the [3.2.1]propellane (**2**) and the [2.2.2]propellane (**3**). The low reactivity of **2** is readily understood since its cleavage to 1,3-dimethylenecyclohexane is orbital symmetry forbidden.[3,4] The high reactivity of **3** has been explained by involving an antibonding diradical intermediate which can open to 1,4-dimethylenecyclohexane in an orbital symmetry allowed reaction.[4,5,6] Alternately, this reactivity may simply be a reflection of the greater strain present in **3** (relative to **2**) which allows the cleavage to proceed via the symmetry forbidden pathway. A knowledge of the reactivity of **1** would serve to distinguish between these possibilities.

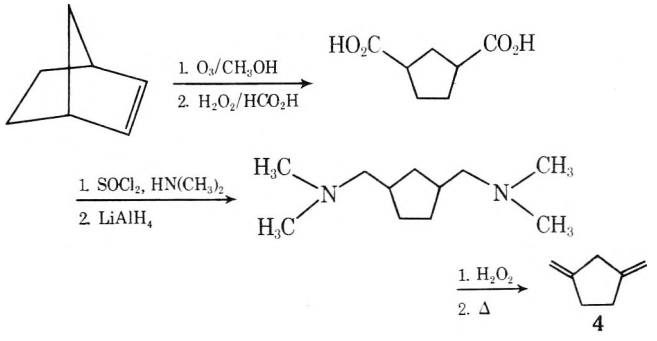


1 **2** **3**

An organometallic derivative of the [2.2.1]propellane has been prepared[7] but neither the hydrocarbon nor any of its simple derivatives have, as yet, been reported. In view of the successful electrochemical ring closures of 1,5-dibromobicyclo[3.2.1]octane to **2**[8] and 1,4-dibromobicyclo[2.2.2]octane to **3**,[9] we have investigated the reduction of 1,4-dibromonorbornane. A suggestion that this approach might be fruitful is found in the work of Wilcox and Leung, who showed that 1,4-dichloronorbornane reacts with lithium to give the 1,4-dilithio derivative but no 4-chloro-1-norbornyllithium.[10]

The conversion of the readily obtained 1,4-dichloronorbornane[11] to the 1,4-dibromo derivative was effected using aluminum foil and a catalytic amount of bromine in methylene bromide.[12] The 1,4-diiodo derivative was prepared in a similar manner from the dichloride by reaction with aluminum foil and a catalytic amount of bromine in methylene iodide.[12] In anticipation of the need for a sample of the ring-opened isomer of **1** for comparison with products resulting from reduction of 1,4-dihalonorbornanes, an authentic sample of 1,3-dimethylenecyclopentane (**4**) was prepared according to Scheme I.

Scheme I



4

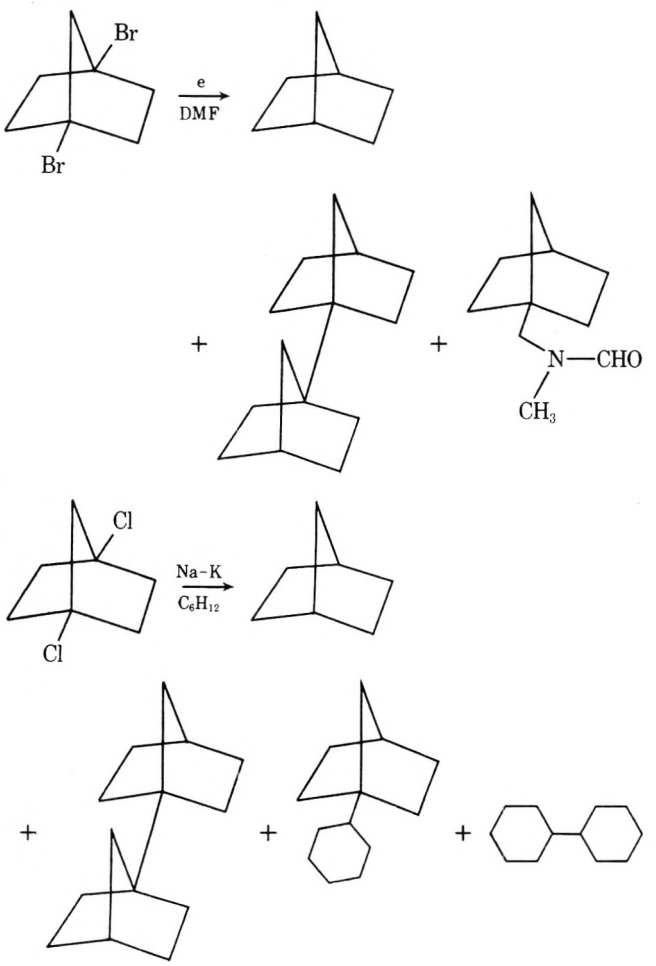
The electrochemical reduction of 1,4-dibromonorbornane was effected at a platinum electrode in dimethylformamide solution at −20 to −30 °C using tetraethylammonium bromide as the supporting electrolyte. The potential was maintained at −2.50 V vs. a mercury pool reference electrode.[13] The products of the reduction were norbornane, 1,1′-binorbornane, and a compound derived from the coupling of a norbornyl radical and dimethylformamide [tentatively assigned as *N*-methyl-*N*-(1-norbornylmethyl)formamide].[14] No 1,3-dimethylenecyclopentane was found, although a priori it could have formed either by thermal cleavage of **1** (if it had been produced) or via a Grob fragmentation[15] of the dibromide precursor. The possibility that **1** had been produced and had existed for a finite time in solution was investigated by repeating the electrolysis and saturating the catholyte with chlorine gas at −30 °C. The addition of chlorine across the C(1)–C(4) bond of any [2.2.1]propellane produced electrochemically is expected to be facile since both the [3.2.1]propellane and the [2.2.2]propellane readily add halogen across the central bond under analogous conditions.[3,5,9] Unfortunately, no 1,4-dichloronorbornane was detected in the product mixture.

The products resulting from the electrochemical reduction of 1,4-dibromonorbornane are similar to those formed when 1,4-dichloronorbornane is reduced with sodium–potassium alloy in cyclohexane; i.e., norbornane, 1,1′-binorbornane, and radical-coupling products[3] (Scheme II). The reactions themselves are analogous in than reduction is accomplished at a surface in both instances and the medium is, therefore, heterogeneous. It is perhaps somewhat surprising that the 1,4-dihalonorbornanes show no tendency to undergo Grob fragmentation under these conditions since the C–X bonds are locked in a conformation which should allow for facile fragmentation.[15] A rationale for the reluctance of 1,4-dihalonorobornanes to undergo Grob fragmentation has been advanced by Gleiter, Stohrer, and Hoffmann[4,16] in terms of the symmetry properties of the interacting orbitals. According to these authors, there is a symmetry imposed barrier to fragmentation of the intermediate in such reductions (be it the 1,4-diradical[4] or the 4-halo-1-anion[16]) due to the bonding nature of the interaction between the orbitals on C(1) and C(4) ("through-space coupling").[3,15]

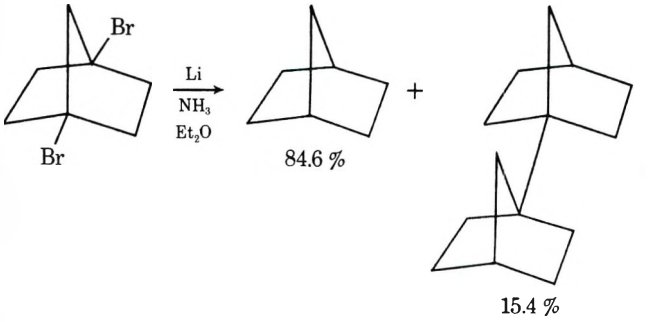
The formation of dimers and radical products in the reduction of 1,4-dihalonorbornanes at a surface may result from either free-radical coupling at the surface or from the formation of the [2.2.1]propellane followed by its rapid reaction with a norbornyl radical. It did not appear possible to distinguish between these possibilities and, therefore, we have attempted to effect the electron transfer under apparently homogeneous conditions.

The reduction of 1,4-dibromonorbornane with lithium in a mixture of ammonia and ether proceeded rapidly at −33 °C. The products of the reaction were norbornane (84.6%), 1,1′-binorbornane (15.4%), and traces of higher polymers (Scheme III). The reduction of the dichloro and diiodo derivatives as

Scheme II



Scheme III



+ trimer and tetramers

well as the 1-halonorbornanes also was studied giving the results summarized in Table I. Contrary to our initial expectations, the reduction of 1-bromo- and 1-iodonorbornanes produced significant amounts of 1,1′-binorbornane (3.9 and 4.3%, respectively).

If the reduction medium were truly homogeneous the formation of 1,1′-binorbornane could not reasonably be due to coupling of norbornyl radicals. The concentration of solvated electrons in the reaction medium was high since a large excess of lithium metal was used. Thus, any radicals formed from the initial electron transfer would be expected to add a second electron, at diffusion controlled rates,[17] to form the bridgehead anion. It should be noted that whereas the 1-norbornyl radical is relatively unstable,[18] the 1-norbornyl anion appears to possess unusual stability.[19,20]

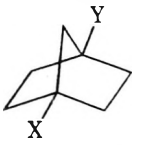
In order to test the radical-coupling hypothesis, two experiments were performed. In the first the lithium–ammonia solution was added to a solution of 1-bromonorbornane in a mixture of ammonia and ether (inverse addition). In this case the proportion of dimer increased from 3.9% to 9.4%. In the other experiment, 1-bromonorbornane was dissolved in a mixture of ammonia and ether and added slowly to a large volume of the lithium in ammonia–ether solution. In this experiment the proportion of dimer formed decreased markedly from 3.9% to 0.8%. Thus the formation of dimer and higher polymers is dependent on the concentration of norbornyl halide during the reduction.

Since it is unlikely that the concentration of radicals in the solution will be high enough to permit significant coupling, the observed concentration effect must have a more complex origin. One reasonable possibility is the formation of hydrophobic regions in the hydrogen-bonded medium, similar to the formation of micelles in water. As the concentration of halide is increased, the number of halide molecules in a given hydrophobic region would increase, permitting more facile radical coupling in the local environment.

Coupling of alkyl halides in metal–ammonia reductions has been observed previously,[21] as well as solvent effects[22] similar to those found in this investigation. The coupling has been proposed to proceed either via the coupling of radicals or by the formation of a carbanion which then effects an SN2 displacement.[22] In the case of the bridgehead halides, the latter mechanism is not possible, and radical coupling is the only reasonable process. It appears that solvent effects on the coupling reaction may generally be explained by our hypotheses.

In any event, it is clear that the results of the electrochemical and metal–ammonia reduction of the 1,4-dihalonorbornanes do not provide evidence either for or against the formation of the [2.2.1]propellane as an intermediate in the reactions. Other types of experiments will be necessary to settle this question.

Table I. Products from the Lithium in Ammonia Reductions of Norbornyl Halides



Registry no.	Halide[a]	Norbornane, %	1,1′-Binorbornane, %
765-67-3	X = Cl; Y = H	100.0	
13474-70-9	X = Br; Y = H	96.1	3.9
930-80-3	X = I; Y = H	95.7	4.3
2941-51-7	X = Y = Cl	99.7	0.3
40950-22-9	X = Y = Br[b]	84.6	15.4
40950-21-8	X = Y = I[b]	80.8	19.2
	X = Br; Y = H (inverse addition)[c]	90.6	9.4
	X = Br; Y = H (high dilution)[c]	99.2	0.8

[a] Solutions were initially 0.50–0.54 M lithium in ammonia–ether and 0.050–0.054 M halide in ammonia–ether. The halide was 0.1–0.5 M in ether prior to addition to lithium in ammonia. [b] Trimers and tetramers were also detected. See Experimental Section. [c] See Experimental Section.

Experimental Section

Melting points were determined on a Hoover-Thomas melting point apparatus and are uncorrected. Boiling points are uncorrected. Proton magnetic resonance spectra were recorded on a JEOL JNM-MH-100 spectrometer. Mass spectra were recorded on a Hitachi RMU-6 instrument. Preparative GLC was effected with an Aerograph A-90-P chromatograph equipped with 0.25-in. columns. Microanalyses were performed by Atlantic Microlab, Inc.

Literature procedures were followed in the preparation of 1-chloronorbornane,[23] 1-bromonorbornane,[24] 1-iodonorbornane,[20] and 1,4-dichloronorbornane.[11]

1,4-Dibromonorbornane. Following the general procedure of McKinley, Pincock, and Scott,[12] narrow strips of common aluminum foil (683.2 mg, 25.30 mmol) were placed in a 200-ml round-bottomed flask filled with a magnetic stirrer, immersion thermometer, and reflux condenser with drying tube. To this flask was added 240 ml of methylene bromide and 400 μl (7.8 mmol) of bromine. The mixture was heated on an oil bath at 80 °C for 1 h during which time the aluminum reacts to form a red-black suspension. The suspension was allowed to cool to room temperature and 2.00 g (12.12 mmol) of 1,4-dichloronorbornane[11] was added at once. The mixture was heated at 95–97 °C on a steam bath for 1 h. The contents of the flask were poured over 200 g of crushed ice and the organic layer washed successively with 100 ml of water, 100 ml of 10% aqueous sodium hydroxide, and 100 ml of brine. After drying ($MgSO_4$), the solvent was removed at reduced pressure to give a black, tarry residue which was sublimed at 55 °C (11–20 mm) to afford white needles, mp 73.5–74 °C (lit.[12] 73 °C) in yields of 68–81%: ^1H NMR ($CDCl_3$) δ 2.07 and 2.25 (AB pattern with further coupling, J_{AB} = 8.0 Hz, 2 H), 2.36 (s, 2 H).

Anal. Calcd for $C_7H_{10}Br_2$: C, 33.1; H, 4.0; Br, 62.9. Found: C, 33.0; H, 4.0; Br, 63.1.

1,4-Diiodonorbornane. Following the general procedure described above,[12] a mixture of 683.2 mg (25.30 mmol) of aluminum foil, 50 ml of methylene iodide, and 254 μl (5.06 mmol) of bromine was heated at 60 °C for 1 h. After cooling to room temperature, 2.00 g (12.12 mmol) of 1,4-dichloronorbornane was added at once and the mixture was heated at 95–97 °C on a steam bath for 1 h. After the workup described above, sublimation of the tarry residue gave 70–74% of the diiodide: mp 102–103 °C (lit.[12] 101 °C); ^1H NMR ($CDCl_3$) δ 2.01 and 2.25 (AB pattern with further coupling, J_{AB} = 8.0 Hz, 8 H), 2.40 (s, 2 H).

Anal. Calcd for $C_7H_{10}I_2$: C, 24.1; H, 2.9; I, 73.0. Found: C, 24.1; H, 2.9; I, 72.9.

***cis*-Cyclopentane-1,3-bis(*N,N*-dimethylcarboxamide).** *cis*-Cyclopentane-1,3-dicarboxylic acid[25] (75.8 g, 0.1 mol) was heated under gentle reflux with 70 g (0.59 mol) of thionyl chloride for 6 h. The excess thionyl chloride was removed under reduced pressure and the dark residue distilled to give 16.2 g (83%) of the acid chloride, bp 79–88 °C (0.35 mm), ir $\nu_{C=O}$ 1785 cm^{-1}.

This acid chloride (16.2 g, 83 mmol) was dissolved in 50 ml of anhydrous ether and added dropwise to a stirred solution of 50 g of dimethylamine in 200 ml of ether cooled to −20 °C. The mixture was allowed to warm to room temperature and stirred overnight. The precipitated amine hydrochloride was removed by filtration and washed with ether. The combined filtrate and washings were diluted with 50 ml of chloroform (controls had shown that the diamide was only slightly soluble in ether) and dried ($MgSO_4$). Evaporation of the solvent afforded 14.3 g (80%) of a semisolid mass containing both the cis and trans isomers of the product. The solid isomer was removed by filtration and sublimed at 80 °C (1 mm) to give 8.0 g of crystals, mp 79.8–82 °C. The liquid isomer was distilled [bath temperature 180 °C (0.2 mm)] to give a colorless oil: ^1H NMR solid isomer ($CDCl_3$) δ 1.7–2.2 (m, 4 H), 2.92 (s, 6 H), 3.10 (s, 6 H), 3.0–3.2 (m, 2 H); liquid isomer ($CDCl_3$) δ 1.7–2.2 (m, 4 H), 2.92 (s, 6 H), 3.12 (s, 6 H), 3.0–3.2 (m, 2 H).

Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.2; H, 9.5; N, 13.2. Found: C, 62.0; H, 9.6; N, 13.1.

1,3-Bis(dimethylaminomethyl)cyclopentane. A Soxhlet extractor was charged with 10.0 g (46.8 mmol) of the bisamide and the amide was slowly leached into a stirred, gently refluxing suspension of 2.81 g of lithium aluminum hydride in 350 ml of anhydrous ether over an 8-h period. The mixture was hydrolyzed by dropwise sequential addition of 2.8 ml of water, 2.8 ml of 15% aqueous sodium hydroxide, and 8.4 ml of water. The mixture was filtered, the filtrate concentrated, and the residue distilled to give 6.45 g (75%) of product, bp 80–81 °C (4.4 mm). An analytical sample was prepared by GLC on a 2.5-ft, 30% SE-30 on Chromosorb P (60–80 mesh) column at 105 °C: ^1H NMR (CCl_4) δ 0.8–1.8 (m, 8 H), 2.17 (s, 12 H).

Anal. Calcd for $C_{11}H_{24}N_2$: C, 71.7; H, 13.1; N, 15.2. Found: C, 71.4; H, 13.2; N, 15.2.

1,3-Dimethylenecyclopentane. A solution of 6.00 g (32.55 mmol) of 1,3-bis(dimethylaminomethyl)cyclopentane in 18 ml of 30% hydrogen peroxide was stirred at room temperature for 40 h. Excess hydrogen peroxide was decomposed by adding 50 mg of platinum black and stirring for an additional 6 h. The mixture was filtered and concentrated at 0.2–1.0 mm (temperature <40 °C) to afford a viscous oil. A small amount (ca. 20 mg) of hydroquinone was added to the oil and the mixture was heated on an oil bath maintained at 180–190 °C (130–150 mm). The pyrolysate was collected in a dry ice cooled trap. Following the pyrolysis, 5 ml of pentane was added to the trap and the pentane-immiscible portion was discarded. The organic layer was washed successively with 2 ml of water, two 2-ml portions of 5% aqueous hydrochloric acid, 2 ml of water, and 2 ml of brine. The pentane solution was cooled to −77 °C and decanted from the ice. This dry solution was concentrated at atmospheric pressure and the residue distilled to give 2.01 g (92.5%) of the diene: bp 102 °C; ir (neat) 3050 (s), 1655 (s), and 870 cm^{-1} (s); ^1H NMR (CCl_4) δ 2.42 (apparent singlet, 4 H), 3.01 (broad s, 2 H), 4.88 (nearly equivalent $=CH_2$, 4 H).

Anal. Calcd for C_7H_{10}: C, 89.3; H, 10.7. Found: C, 89.4; H, 10.6.

Electrochemical Reduction of 1,4-Dibromonorbornane. The electrolysis cell was constructed from a 700-ml beaker fitted with a magnetic stirrer, cooling bath, and a four-hole rubber stopper to accommodate the anode, cathode, reference electrode, and nitrogen inlet–outlet tube. The cathode (purchased from the Arthur H. Thomas Co.) consisted of a reinforced platinum gauze cylinder (45 mesh, 2 in. high by 1 in. diameter) with a connecting platinum wire. The anode consisted of a coiled platinum wire dipping into background electrolyte and separated from the cathodic cell by means of a salt bridge prepared from methyl cellulose and electrolyte solution as described by Dryhurst and Elving.[26] The potential was controlled relative to a mercury pool reference electrode by means of a Wenking 61 RS potentiostat.

The electrolysis cell was charged with 500 ml of 0.1 M tetraethylammonium bromide in dry dimethylformamide[27] and 635 mg (2.5 mmol) of 1,4-dibromonorbornane was added. A constant stream of nitrogen was passed through the stirred solution and the cell was maintained at −20 to −30 °C throughout the electrolysis. A potential of −2.50 V vs. a mercury pool was maintained (current 100–140 mA) for 7–8 h. The catholyte was diluted with an equal volume of cold, saturated aqueous sodium chloride and extracted with two 250-ml portions of pentane–ether. The organic extract was washed with water, dried ($MgSO_4$), and concentrated. GLC analysis of the residue on a 10 ft, 30% SE-30 on Anakrom M (60–80 mesh) column at 119 °C indicated that no 1,3-dimethylenecyclopentane had been produced. Three products were detected in addition to short retention time components derived from reduction of dimethylformamide and the supporting electrolyte. The shortest retention time product was identified as norbornane by coinjection with an authentic sample. The longest retention time product was collected and sublimed at 80 °C (20 mm) to give a solid, mp 109–111 °C, having a mass spectrum identical with that of 1,1′-binorbornane[28] (lit.[29] mp 111–112.5 °C). The intermediate retention time product was not isolated in sufficient quantity to permit unambiguous characterization. On the basis of its spectral properties the compound appears to have been derived from DMF and a norbornyl radical.[30]

In a separate experiment, the electrolysis was run as described above and the catholyte saturated with chlorine gas at −30 °C. After standing at −30 °C overnight the dimethylformamide solution was worked up. GLC analysis revealed the presence of the products described above. No 1,4-dichloronorbornane was detected.

Lithium in Ammonia Reduction of Norbornyl Halides. Experiments were conducted such that the initial concentrations would be 0.50–0.54 M lithium in ammonia–ether and 0.050–0.054 M halide in ammonia–ether. Typically, 2 mmol of the halide in dry diethyl ether (0.1–0.5 M solutions) was added to a rapidly stirred solution of 20 mmol of lithium in twice distilled ammonia[31] cooled to −78 °C. The cooling bath was removed and the mixture was stirred at reflux for 1 h. Reductions were quenched by cautious addition of solid ammonium chloride to discharge the characteristic blue color. The ammonia was allowed to evaporate and the ethereal solution was washed successively with water, 5% aqueous hydrochloric acid, and brine. The solution was dried ($MgSO_4$) and analyzed by gas chromatography on a Perkin-Elmer Model 900 chromatograph equipped with flame ionization detector and interfaced with a Hewlett-Packard 3370A integrator. Product yields were determined on a 10 ft, 30% SE-30 on Anakrom μ (60–80 mesh) column with linear temperature programming from an initial temperature of 80 °C for 8 min to 210 °C at a rate of 6.5 °C/min. Area ratios were corrected to mole ratios with the response factors determined for norbornane and 1,1′-binorbornane under identical conditions. Results are given in Table I.

The solutions resulting from reduction of 1,4-dibromo- and 1,4-diiodonorbornane were concentrated to dryness and subjected to sublimation to remove norbornane and 1,1′-binorbornane. Analysis of the residues by mass spectroscopy revealed parent peaks (*m/e* 378 and 284) and fragmentation patterns expected for the trimer [1-(1-norbornyl)-4-(1-norbornyl)norbornane] and the tetramer[4,4′-di-(1-norbornyl)-1,1′-binorbornane].

Lithium in Ammonia Reduction of 1-Bromonorbornane with Inverse Addition. A solution of 134.8 mg (19.5 mmol) of lithium metal in 60 ml of twice-distilled ammonia[31] was added dropwise to a rapidly stirred solution of 351.1 mg (2.00 mmol) of 1-bromonorbornane in 50 ml of doubly-distilled ammonia and 10 ml of dry diethyl ether. The characteristic blue color of lithium in ammonia was immediately discharged upon addition to the halide solution. Following the addition, excess lithium was destroyed with solid ammonium chloride as described above. GLC analysis of the ethereal residue revealed 90.6% norbornane and 9.4% 1,1′-binorbornane.

Lithium in Ammonia Reduction of 1-Bromonorbornane at High Dilution. A solution of 500 mg (2.86 mmol) of 1-bromonorbornane in 50 ml of dry diethyl ether was diluted with 150 ml of twice-distilled ammonia[31] and added dropwise to a rapidly stirred solution of 250 ml (35.7 mmol) of lithium in a mixture consisting of 500 ml of twice-distilled ammonia[31] and 100 ml of dry diethyl ether at reflux. Following the addition, the reaction mixture was allowed to stir for 1 h at reflux and was then quenched with solid ammonium chloride as described above. GLC analysis of the ethereal residue revealed 99.2% norbornane and 0.8% 1,1′-binorbornane.

Registry No.—**4**, 59219-48-6; *cis*-cyclopentane-1,3-dicarboxylic acid, 876-05-1; *cis*-cyclopentane-1,3-dicarboxylic acid chloride, 59219-49-7; *cis*-cyclopentane-1,3-bis(*N*,*N*-dimethylcarboxamide), 59219-50-0; *trans*-cyclopentane-1,3-bis(*N*,*N*-dimethylcarboxamide), 59219-51-1; 1,3-bis(dimethylamino)cyclopentane, 59219-52-2; *N*-methyl-*N*-(1-norbornylmethyl)formamide, 59219-53-3; lithium, 7439-93-2; ammonia, 7664-41-7.

References and Notes

(1) This investigation was supported by a grant from the National Science Foundation.
(2) To whom correspondence should be addressed.
(3) K. B. Wiberg and G. J. Burgmaier, *J. Am. Chem. Soc.*, **94**, 7396 (1972).
(4) W.-D. Stohrer and R. Hoffmann, *J. Am. Chem. Soc.*, **94**, 779 (1972).
(5) P. E. Eaton and G. H. Temme III, *J. Am. Chem. Soc.*, **95**, 7508 (1973).
(6) M. D. Newton and J. M. Schulman, *J. Am. Chem. Soc.*, **94**, 4391 (1972).
(7) M. E. Jason, J. A. McGinnety, and K. B. Wiberg, *J. Am. Chem. Soc.*, **96**, 6531 (1974).
(8) M. R. Rifi, *Collect. Czech. Chem. Commun.*, **36**, 932 (1971).
(9) K. B. Wiberg, G. A. Epling, and M. Jason, *J. Am. Chem. Soc.*, **96**, 912 (1974).
(10) C. F. Wilcox and C. Leung, *J. Org. Chem.*, **33**, 877 (1968).
(11) A. P. Marchand and W. R. Weimar, Jr., *J. Org. Chem.*, **34**, 1109 (1969).
(12) J. W. McKinley, R. E. Pincock, and W. B. Scott, *J. Am. Chem. Soc.*, **95**, 2030 (1973).
(13) The mercury pool reference electrode has been shown to be a stable reference in dimethylformamide solution [P. H. Given and M. E. Peover, *J. Chem. Soc.*, 1602 (1959)] and is about 0.5 V cathodic of a saturated calomel electrode. The electrolyses were carried out at the most negative potential the solvent would permit since we have shown that such potentials favor ring closure [K. B. Wiberg and G. A. Epling, *Tetrahedron Lett.*, 1119 (1974)].
(14) See Experimental Section.
(15) (a) C. A. Grob and P. W. Schiess. *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967); (b) C. A. Grob, *ibid.*, **8**, 535 (1969); (c) C. A. Grob, W. Kunz, and P. R. Marbet, *Tetrahedron Lett.*, 2613 (1975).
(16) R. Gleiter, W.-D. Stohrer, and R. Hoffmann, *Helv. Chim. Acta*, **55**, 893 (1972).
(17) J. Jacobus and J. F. Eastham, *Chem. Commun.*, 138 (1969).
(18) (a) D. E. Applequist and L. Kaplan, *J. Am. Chem. Soc.*, **87**, 2194 (1965); (b) J. P. Lorand, S. D. Chodroff, and R. W. Wallace, *ibid.*, **90**, 5266 (1968); (c) R. C. Fort, Jr., and R. E. Franklin, *ibid.*, **90**, 5267 (1968); (d) L. B. Humphrey, B. Hodgson, and R. E. Pincock, *Can. J. Chem.*, **46**, 3099 (1968).
(19) P. T. Lansbury and J. D. Sidler, *Tetrahedron Lett.*, 691 (1965).
(20) P. T. Lansbury, V. A. Pattison, J. D. Sidler, and J. B. Bieber, *J. Am. Chem. Soc.*, **88**, 78 (1966).
(21) G. W. Watt, *Chem. Rev.*, **46**, 317 (1950).
(22) A. Beverloo, M. C. Dieleman, P. E. Verkade, K. S. deVries, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **81**, 1033 (1962); P. E. Verkade, K. S. deVries, and B. M. Wepster, *ibid.*, **83**, 1149 (1964).
(23) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *J. Am. Chem. Soc.*, **83**, 3998 (1961).
(24) K. B. Wiberg and B. R. Lowry, *J. Am. Chem. Soc.*, **85**, 3188 (1963).
(25) R. H. Perry, Jr., *J. Org. Chem.*, **24**, 829 (1959).
(26) G. Dryhurst and P. J. Elving, *Anal. Chem.*, **39**, 607 (1967).
(27) The dimethylformamide was purified by stirring over barium oxide and distillation from barium oxide, in vacuo, prior to use.
(28) We thank Dr. K. Shen for providing us with a sample of 1,1′-binorbornane.
(29) R. A. Alden, J. Kraut, and T. G. Traylor, *J. Am. Chem. Soc.*, **90**, 74 (1968).
(30) This product is tentatively assigned the structure depicted in Scheme II [*N*-methyl-*N*-(1-norbornylmethyl)formamide)] on the basis of the following spectral properties: MS *m/e* 167 (M^+), 138 (M^+ − CHO), 95 (base), 72 (M^+ − norbornyl); ir (CCl_4) 2840 (m), 1630 cm^{-1} (s); ^1H NMR (CCl_4) δ 1.3–2.05 (m, 10), 2.1–2.3 (m, 1), 3.06 (s, 5 H).
(31) Ammonia was first distilled from the tank into a flask containing lithium metal and then from the lithium metal into the reaction vessel.

Displacement of an Alkyl Group from Quaternary Ammonium Chlorides by Certain Neutral Nucleophiles

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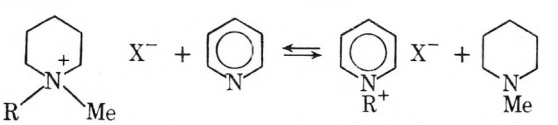
Heating $(Me_3SiO)_3Si(CH_2)_3Cl$ with excess trimethylamine caused almost quantitative yields of $(Me_3SiO)_3Si(CH_2)_3NMe_2$ and $Me_4N^+Cl^-$. Some conditions influencing the yields of products from alkyl chlorides and tertiary amines were studied. One alkyl group can be displaced from quaternary salts easily at 100 °C in nonpolar media by neutral nucleophiles with the following approximate order of reactivity: $NH_3 \leq RSH < HOAc < RNH_2 < R_2NH < R_3N$.

Recently we heated 3-[tris(trimethylsiloxy)silyl]propyl chloride (I) with an excess of trimethylamine expecting to obtain 3-[tris(trimethylsiloxy)silyl]propyltrimethylammonium chloride (III),[1] but obtained instead 3-[tris(trimethylsiloxy)silyl]propyldimethylamine (II) and tetramethylammonium chloride in almost quantitative yield. Dr. C. L. Frye of this laboratory suggested that these products might be an example of a type IV, SN2 reaction, the first example of which was described by Hughes and Whittingham[2] in 1960:

$$Ph_2MeNMe^+ + Me_3N \rightarrow Me_3NMe^+ + Ph_2MeN$$

This type of reaction had been predicted in 1935[3] and many examples have been found since 1960 in which an alkyl group is transferred to an uncharged nucleophile from an onium ion, including ions such as sulfonium, oxonium, or halonium ions.

Hutchinson and Tarbell[4] in 1969 showed that the reaction for ammonium ions was reversible and they studied the equilibrium



R = $PhCH_2$, X = Cl; R = $PhCH_2$, Me, X = Cl, Br

They found that (1) water prevented the reaction even at 140 °C; (2) bromides reacted faster than chlorides; (3) equilibria were reached most rapidly in nonpolar solvents; (4) a

Table I. Products From 3-[Tris(trimethylsiloxy)silyl]propyl Chloride and Trimethylamine

$$RCl(I) + Me_3N \rightarrow RN^+Me_3Cl^-(III) \overset{Me_3N}{\rightleftarrows} RNMe_2(II) + Me_4N^+Cl^-$$

$$R = (Me_3SiO)_3SiCH_2CH_2CH_2-$$

	Mol of NMe_3/RCl	Solvent	Time, h	Temp, °C	Mol % I	Mol % III	Mol % II
1	2.4	None	129	130			>98
2	1.66	None	164	110		50	50
3	2.5	None	20	150			>95
4	1	None	1.25	150	50	25	25
5	2.2	30% Me_2CHOH by volume	3	100	61	39	
6	2.2	30% Me_2CHOH by volume	7.5	100	24	76	
7	2.2	30% Me_2CHOH by volume	69	100		21	79
8	2.2	30% Me_2CHOH by volume	144	100		21	79
9	7.5	70% heptane by volume	3	160	>97		

Table II. Ammonium Ions + Nucleophiles → Products

$$R_4N^+ + Nucl \rightarrow R_3N + R \cdot Nucl^+$$

	Mol ratio of ion/nucl	Ion	Nucl	Registry no.	Time, h	Temp, °C	Products (% yield)[a]
1	3	NH_4^+	n-Bu_3N	102-82-9	17.5	160	No detectable change
2	1	$PhCH_2NC_5H_5^+$	n-Bu_2NH	111-92-2	18	155	C_5H_5N, $PhCH_2NBu_2$ (100)
3	1	$PhCH_2NC_5H_5^+$	n-$BuNH_2$	109-73-9	18	155	C_5H_5N, $PhCH_2NHBu$ (75)
4	1	III	n-Bu_2NH		18	155	$(Me_3SiO)_3Si(CH_2)_3NBu_2$ (19)[b] Me-Bu_2N (II) (81)[b]
5	1	III	n-$BuNH_2$		18	155	$(Me_3SiO)_3Si(CH_2)_3NHBu$ (13)[b] MeBuNH (II) (87)[b]
6	1	$PhCH_2NC_5H_5^+$	NH_3	7664-41-7	1.3	150	C_5H_5N, $PhCH_2NH_2$ (23)
7	1	$PhCH_2NC_5H_5^+$	n-$BuNH_2$		1.3	150	C_5H_5N, $PhCH_2NHBu$ (57)
8	1	$PhCH_2NC_5H_5^+$	n-Bu_2NH		1.3	150	C_5H_5N, $PhCH_2NBu_2$ (91)
9	1	$PhCH_2NC_5H_5^+$	n-Bu_3N		1.3	150	C_5H_5N, $PhCH_2NBu_3^+$ (100)[c]
10	1	$PhCH_2NC_5H_5^+$	$C_{12}H_{25}SH$	112-55-0	1.3	150	C_5H_5N, $PhCH_2SC_{12}H_{25}$ (33)
11	1	$PhCH_2NC_5H_5^+$	CH_3COOH	64-19-7	1.3	150	C_5H_5N, $PhCH_2OAc$ (47)

[a] % yield was calculated from GLC analysis of products (see Experimental Section). [b] Products were treated with NaOH, extracted with ether, analyzed by GLC, and identified by GLC–mass spectrometry. [c] This product was extracted with ether; C_5H_5N was identified by GLC of extract. Crystalline $PhCH_2NBu_3^+Cl^-$ was dried, weighed, titrated for Cl^- with $AgNO_3$, Cl^- equivalent 311.8 (calcd 311.94).

benzyl group exchanged more rapidly than did a methyl group; (5) equilibrium constants were nearly the same for bromides or chlorides.

The effects of such equilibria during syntheses of quaternary ammonium salts from alkyl halides and tertiary amines have not been described.

Table I shows some effects of temperature, solvents, time, and molar ratio of reagents upon the products formed from trimethylamine and I.

The products in Table I are explained as the result of two consecutive reactions, the first being practically irreversible below about 175 °C:[5] III heated in heptane above 100 °C for 48 h was recovered quantitatively and unchanged as should be expected if step 1 is irreversible under these conditions. Step 2, however, is highly reversible and leads to equilibrium mixtures of quaternary salts.

Although precipitation of $Me_4N^+Cl^-$ can drive these reactions to completion in nonpolar media, the use of a polar solvent in which $Me_4N^+Cl^-$ remains dissolved afforded the expected equilibrium mixtures. Thus, in 30% by volume 2-propanol, an equilibrium was reached with 21% III and 79% II at a Me_3N/RCl ratio of 2.2 at 100 °C. The high concentration of III at 7.5 h indicates that step 1 was much faster than step 2 in this solvent. In 70% by volume heptane almost no reaction took place in 3 h at 160 °C.

Benzylpyridinium chloride and III were found to be of approximately the same reactivity toward n-butyl- and di-n-butylamines. Benzylpyridinium chloride was heated with various nucleophiles to gain some qualitative data about the relative effectiveness of nucleophiles. See Table II.

Apparently an amine hydrochloride will not transfer an alkyl group. In our brief study the quaternary ammonium salts transferred an alkyl group to uncharged nucleophiles which included ammonia, a primary, a secondary, or a tertiary amine, a thiol, and acetic acid.

Experiment 9 in Table II indicates that pyridine must be a surprisingly ineffective nucleophile judging from the near quantitative formation of $PhCH_2NBu_3^+Cl^-$.

The 4th and 5th examples of Table II demonstrate that a methyl group transfers to certain nucleophiles more readily than does a $(Me_3SiO)_3Si(CH_2)_3-$ group, and both compete in these reactions.

The yields of products from benzylpyridinium chloride with a series of nucleophiles in no solvent under similar conditions would suggest the following approximate order of reactivity: $NH_3 \leq RSH < HOAc < n\text{-}BuNH_2 < n\text{-}Bu_2NH < n\text{-}Bu_3N$.

Experimental Section

Reagents. 3-[Tris(trimethylsilyl)propyl] chloride (I) was prepared by a published procedure.[6] All other reagents were reagent grade commercial products.

All gas–liquid chromatographs were obtained with an F & M Model 500 gas chromatograph with a 6 ft × 0.25 in. stainless steel column packed with 5% Dow Corning 200 gum on Anakrom ABS 60–70 mesh,

treated with hexamethyldisilazane and programmed from 50 to 300 °C at 30 °C/min.

All mass spectra were recorded with an AEI MS-30 dual beam mass spectrometer interfaced to an AEI DX-50 data system.

Procedures. All experiments were done with sealed containers. Large-scale experiments were done with a 1.4-l. 316 stainless steel autoclave. Others were done in sealed Pyrex glass tubes. A typical example for expt 1 and 3 in Table I follows.

The autoclave was charged with I (707.9 g, 1.9 mol) and trimethylamine (265 g, 4.5 mol) was added from a small steel sampling bottle. The mixture was heated to 130 °C for 129 h and cooled to room temperature. Trimethylamine was then permitted to escape into a trap filled with dilute hydrochloric acid. The products were vacuum filtered to yield 223.6 g of crystalline solids. These were washed with hexane, dried under vacuum, and titrated potentiometrically in water for chloride ion. Found: 109.5 mg/mequiv (calcd for $Me_4N^+Cl^-$, 109.60 mg/mequiv). The filtrate was >98 area % of one compound. The filtrate was distilled to obtain 641.1 g (88% yield), bp 106–107 °C (3 mmHg), $n^{25}D$ 1.4086, neut equiv 382.2 mg/mequiv (calcd for $(Me_3SiO)_3Si(CH_2)_3NMe_2$ (II),[7] $Si_4C_{14}H_{39}O_3N$, 381.8).[7] The distilled product was one sharp peak on GLC and was taken as a standard for subsequent analyses.

The analysis of example 4 of Table I illustrates how mixtures were analyzed when they contained I, II, and III at the end of the experiment.

The product was filtered and the crystalline material was washed with dry hexane, dried, weighed, and titrated for Cl^- with $AgNO_3$. The Cl^- equivalent weight was 269.6 mg/mequiv (calcd for a 1:1 molar mixture of III and $Me_4N^+Cl^-$ 270.61 mg/mequiv). The filtrate and hexane washes were stripped of solvent under vacuum to obtain 14.5 g of a liquid residue, which by GLC was 65.25 wt % I, 0.025 mol, 0.5 of initial charges of I, and 34.7 wt % II. The liquid residue had a base neutral equivalent weight of 1097.1 mg/mequiv which independently indicated ~34.75% II or about 0.013 mol.

Analysis of Examples 7 and 8 (Table I). Various standard solutions of III decomposed in a very reproducible way when injected into our GLC column. III → I + Me_3N + II + MeCl. The ratio of the peak areas of I/II was very close to 1:3.125.

The composition of mixtures that contained both II and III was determined from peak areas measured for I and II. For example, a solution of 1 equiv of I, 2.2 equiv of Me_3N, and 2-propanol, 30% by volume, was heated to 100 °C for 69 h. The tube was then cooled and opened and a sample was injected on the GLC column. The peak areas of I/II were 1/14.9 corresponding to that calculated to result from a mixture of 21% III and 79% II.

The alcohol was stripped from the sample under vacuum. The salts that precipitated were removed by filtration. The filtrate contained no I detectable by GLC. Thus, I observed above in solution had its origin in the thermal decomposition of III.

Analysis of Examples in Table II. Concentrated aqueous NaOH was added to the mixtures to free amines from their hydrochlorides. The mixtures were shaken with a weighed quantity of heptane.

The amount of each amine in the heptane was determined by GLC with heptane as an internal standard.

Registry No.—I, 18077-31-1; II, 29346-33-6; III, 29394-88-5; Me_3N, 75-50-3; $NH_4^+Cl^-$, 12125-02-9; $PhCH_2NC_5H_5^+Cl^-$, 2876-13-3.

References and Notes

(1) K. W. Michael and Y. A. Peters, U.S. Patent 3 719 697 (March 6, 1973).
(2) E. D. Hughes and D. J. Whittingham, *J. Chem. Soc.*, 806–809 (1960).
(3) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 244 (1935).
(4) R. E. J. Hutchinson and D. S. Tarbell, *J. Org. Chem.*, **34**, 67 (1969).
(5) O. Westphal and D. Jerchel, *Ber.*, **73B**, 1002 (1940).
(6) J. W. Ryan, G. K. Menzie, and J. L. Speier, *J. Am. Chem. Soc.*, **82**, 3601 (1960).
(7) H. Maki, Y. Horiguchi, T. Suga, and S. Komori, *Yukagaku*, **19**, 1029–1033 (1970), describe this compound as having bp 105–106 °C (3 mm).

Nuclear Magnetic Resonance Studies. 6. Properties of Phosphorus–Nitrogen Ylides[1]

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The electronic distribution and conformation of triphenylphosphinimines and phosphinazines are discussed in the context of their ^{13}C and ^{31}P NMR parameters. CNDO/2 molecular orbital calculations on model phosphorus–nitrogen ylides are substantially in agreement with these NMR properties. It is found that the barriers of rotation about the N–C and N–N bond in *N*-vinylphosphinimine (17) and formylphosphazine (18), respectively, are small. The lone pairs of electrons on the nitrogen adjacent to phosphorus are delocalized to the methylene carbon in 17 but not in 18. Direct evidence is found for the dissociation of a phosphinazine into triphenylphosphine and the parent diazo compound.

Phosphinimines and phosphazines have been known since 1919[3] and their synthetic utility has been extensively explored.[4] Little, however, is known about the physical properties, conformation, and electron distribution in these phosphorus–nitrogen ylides. In the present work[5] we have examined the ^{13}C and ^{31}P NMR of these ylides and by the use of CNDO/2 molecular orbital calculations[6] information concerning the conformation and electronic nature of these compounds is discussed. The ^{31}P and ^{13}C NMR parameters for a series of *N*-trimethylsilyltrialkylphosphinimines has recently been reported[7] and Hückel π-type calculations have been published with regard to the uv properties of phosphinimines and phosphazines.[8]

NMR Results. The ^{31}P, ^{13}C chemical shifts and ^{13}C–^{31}P couplings are given in Tables I–III, respectively. The ^{31}P chemical shift in Table I of *N*-phenyltriphenylphosphinimine (1) is shielded by 29.0 ppm from its phosphonium salt, **2**. Likewise, the phosphazines are shielded by approximately 20 ppm from their corresponding salts, i.e., compare **9** with **10**. These $\Delta\delta P$ values are somewhat larger than for the isoelectronic benzylidene or allylidenetriphenylphosphoranes (16.2 and 10.1 ppm, respectively).[1] The ^{31}P chemical shift of **1** where the excess negative charge on the nitrogen can be delocalized into the phenyl ring is not much different from that of *N*-trimethylsilyltriphenylphosphinimine (**4**). However, phosphinimines containing a strong electron-withdrawing group adjacent to the nitrogen, i.e., **5** and **6**, are deshielded by 11.6 to 17.6 ppm, respectively, from **1**. The phosphazines in Table I have ^{31}P chemical shifts that are deshielded from **1** by 15.4 to 19.4 ppm. *N*-Tosyltriphenylphosphazide (**14**) is deshielded from its phosphinimine counterpart, **6**, by 14.2 ppm.

The ^{31}P chemical shift of *N*-trityltriphenylphosphinimine (**3**) is shielded with respect to the other phosphinimines. This is presumably a result of steric interactions between the two sets of phenyl rings.[9]

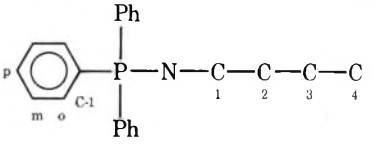
The ^{13}C chemical shift for carbon 4 in *N*-phenyltriphenyl-

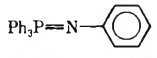
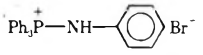
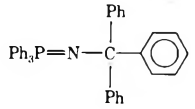
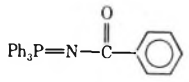
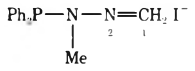
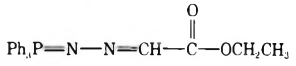
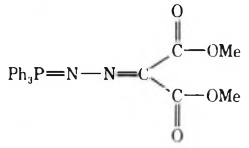
Table I. ^{31}P Chemical Shifts of Phosphinimines, Phosphazines, and Related Compounds

Compd	No.	δP[a]	Registry no.	Compd	No.	δP[a]	Registry no.
$Ph_3P{=}N{-}Ph$	1	3.0	2325-27-1	$Ph_3P{=}N{-}N{=}CH_2$	7	21.4	15990-54-2
$Ph_3\overset{+}{P}{-}NH{-}Ph\ Br^-$	2	32.0	59230-96-5 17490-46-9[c]	$Ph_3\overset{+}{P}{-}N(Me){-}N{=}CH_2\ I^-$	8	47.0	55009-66-0 59230-97-6[c]
$Ph_3P{=}N{-}CPh_3$	3	−10.3	56956-92-4	$Ph_3P{=}N{-}N{=}CPh_2$	9	18.4	1109-01-9
$Ph_3P{=}N{-}SiMe_3$	4	−1.8[b]	13892-06-3	$Ph_3\overset{+}{P}{-}NH{-}N{=}CPh_2\ Br^-$	10	39.3	1109-00-8 59230-98-7[c]
$Ph_3P{=}N{-}C(O)Ph$	5	20.6	17436-52-1	$Ph_3\overset{+}{P}{-}N(Me){-}N{=}CPh_2\ I^-$	11	48.3	1109-43-9 59230-99-8[c]
$Ph_3P{=}N{-}Tos$	6	14.6	1058-14-6	$Ph_3P{=}N{-}N{=}CH{-}CO_2Et$	12	22.4	22610-15-7
				$Ph_3P{=}N{-}N{=}C(CO_2Me)_2$	13	20.9	6085-22-9
				$Ph_3P{=}N{-}N{=}N{-}Tos$	14	28.8	13378-67-1

[a] The ^{31}P chemical shifts are reported in parts per million downfield from external 85% H_3PO_4. The values correspond to those obtained in $CDCl_3$. [b] Value taken from ref 7. [c] Uncharged form.

Table II. ^{13}C Chemical Shifts of Phosphinimines and Phosphazines



Compd	No.	Carbon, ppm[a] 1	2	3	4	5	C-1	o	m	p
	1	151.0	123.4	128.5	117.3		131.2	132.4	128.4	131.5
	2	137.8	123.5	129.2	121.8		119.8	135.5	130.0	135.2
	3	[b]	151.7	126.9	129.2	125.2	135.0	132.4	127.8	130.1
$Ph_3P{=}N{-}SiMe_3$[c]	4	6.1					136.4	132.6	128.7	131.3
	5	176.6	139.5	130.6	127.6	129.5	128.4	133.1	128.6	132.2
$Ph_3P{=}N{-}N{=}CH_2$	7	137.7					129.4	133.2	128.6	132.0
	8	136.6	34.1				118.6	134.1	130.4	135.7
	12	137.8	165.2	59.5	14.4		127.8	133.3	128.7	132.4
	13	139.5	166.6 (163.1)	51.8 (51.5)[d]			[b]	133.4	128.8	132.7

[a] The ^{13}C chemical shifts are reported in parts per million from internal Me_4Si. [b] The resonances were too weak to be observed or obscured by another peak. [c] Values taken from ref 7. [d] Two sets of resonances were observed for carbons 2 and 3.

phosphinimine (1) (Table II) suggest some delocalization of charge onto this carbon by comparison with its amino-substituted phosphonium salt, **2**. Thus, carbon 4 in **1** is shielded by 4.5 ppm from that in **2**. This is a relatively small effect compared to benzylidenetriphenylphosphorane where the value for the corresponding position is 14.5 ppm.[1] The ^{13}C chemical shift of the methylene carbon in formyltriphenylphosphazine (**7**) is slightly deshielded from its phosphonium salt analogue, **8**, and therefore there is little, if any, delocalization of negative charge onto this carbon. This is contrasted by the fact that the analogous carbon in the isoelectronic allylidenetriphenylphosphorane is shielded by 32.4 ppm from its phosphonium salt.[1]

The ^{13}C chemical shifts for the C-1 phenyl carbons in the phosphinimines and phosphazines are similar to those found for the phosphorus–carbon ylides.[1,10] Note that the C-1 phenyl carbons for the phosphorus–nitrogen ylides are deshielded with respect to their phosphonium salt analogues, i.e., compare **1** with **2** and **7** with **8**. The ^{13}C chemical shift of alkyl carbon 1 in **1** is also deshielded in comparison to that found for **2**. This effect which is present for phosphorus–carbon ylides[1] and phosphine oxides may be due, in part, to an electric field effect of the P=X bond.[11]

The ^{13}C chemical shifts of the meta and para carbons are shielded by 1.6 and 3.7 ppm for **1** compared to its phosphonium salt protomer, **2**. A similar situation occurs for **7** and

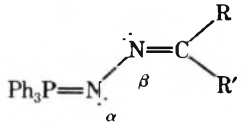
Table III. $^{13}C-^{31}P$ Couplings of Phosphinimines and Phosphazines

Compd	No.	Carbon, Hz[a]					
		1	2	C-1	o	m	p
$Ph_3P{=}N{-}C_6H_5$	1	2.4	17.5	98.7	9.6	11.9	2.8
$Ph_3P{-}NH{-}C_6H_5\ Br^-$	2[b]	2.4	18.3	102.5	11.6	13.4	*
$Ph_3P{=}N{-}C(Ph)_2{-}C_6H_5$	3	c	8.7	101.5	9.9	12.0	2.7
$Ph_3P{=}N{-}SiMe_3$	4[d]	3.2		101.6	10.2	12.0	2.8
$Ph_3P{=}N{-}C(=O){-}C_6H_5$	5	2.4	20.8	99.3	10.1	12.2	2.9
$Ph_3P{=}N{-}N{=}CH_2$	7	45.9		93.6	8.3	11.4	2.7
$Ph_3P{-}N(Me){-}N{=}CH_2\ I^-$	8	6.7	12.2	103.3	11.0	13.4	2.7
$Ph_3P{=}N{-}N{=}CH{-}CO_2Et$	12	48.8	*	94.0	8.5	11.0	2.4
$Ph_3P{=}N{-}N{=}C(CO_2Me)_2$	13	47.6	*	c	8.6	11.0	*

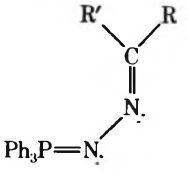
[a] The numbering system used is described in Table II. The digital resolution used was ± 0.1 Hz. An asterisk indicates unresolved coupling. [b] The P–C coupling to carbon 4 was 6.7 Hz. [c] The resonances were too weak to be observed or observed by another peak. [d] Values taken from ref 7.

phosphorus–carbon ylides.[1] This may be taken as evidence that some charge is being transferred from nitrogen to phosphorus if it is assumed that ^{13}C chemical shifts of meta and para phenyl carbons reflect changes in the inductive and resonance properties of substituents.[12]

That only one set of resonances for carbon 2 and 3 were observed for 1 implies rapid rotation about the N–C bond. The phosphazines can also have cisoid (*Z*) or transoid (*E*)



E



Z

geometries. The fact that two carbonyl and methoxy carbon resonances are observed for **13** implies that inversion of the β nitrogen or C–N_β rotation is slow on the NMR time scale at 38 °C. The two methoxyl groups are also nonequivalent by ~10 Hz in the ^1H NMR of **13** up to 65 °C. There is, however, only one methylene carbon for all of the phosphazines reported in Table II. Discounting accidental isochrony,[13] this result implies that interconversion of the *E* and *Z* conformers in the phosphazines is rapid or that one conformer is strongly preferred over the other. There is also only one ^{31}P resonance for **7** and **9** up to 100 °C. Examination of molecular models for **7** reveals that there are steric interactions between the methylene protons and the phenyl rings; however, this is not severe.[15] CNDO/2 molecular orbital calculations on formylphosphazine indicate a low barrier of rotation about the N–N bond with neither conformer strongly favored (vide infra). Molecular orbital calculations on azines and hydrazones also indicate low N–N barriers of rotation.[16] That only one set of ethyl and carbonyl resonances was observed for **12** can be taken to imply that the carboethoxy group is favored in either a syn or anti relationship with respect to the N_β=C bond.

The $^{31}P-^{13}C$ couplings are quite similar to those found for phosphorus–carbon ylides,[1] with the exception of an extraordinarily large $^3J_{P-C}$ found for alkyl carbon in the phosphazines, **7**, **12**, and **13**. It was previously suggested[5] that part of this difference is due to the substitution of an additional nitrogen atom. However, phosphonium salt, **8**, has a $^3J_{P-C}$ which is typical for that found in other ylides and phosphonium salts.[1,9a] Finite perturbation calculations of $^3J_{P-C}$ for model phosphinimines and phosphazines suggest essentially no difference for this coupling.[17]

Molecular Orbital Calculations. In order to ascertain why the phosphazines, and to a smaller extent the phosphinimines, show little delocalization of charge throughout the π framework of the molecules, a series of molecular orbital calculations was carried out on model compounds.[18]

Calculations on *N*-vinylphosphinimine (**17**) were carried out using the geometry reported for *p*-bromo-*N*-phenyltriphenylphosphinimine.[19a] Both CNDO/2 methods (spd and sp) showed the transoid (*E*) geometry of **17** to be more stable than the cisoid (*Z*) by 0.8 and 7.2 kcal/mol, respectively. The barriers of rotation about the N–C bond from the transoid geometry are 1.3 and 7.7 kcal/mol for the CNDO/2 (spd and sp) methods, respectively. Likewise, formylphosphazine (**18**), using the same P–N bond length as **17**,[20] gives barriers of rotation about the N–N bond of 3.7 and 3.6 kcal/mol; with CNDO/2 (spd and sp) starting from the cisoid conformer, CNDO/2 (spd) predicts the cisoid geometry of **18** to be more stable than the transoid by 4.2 kcal/mol, while the CNDO/2 (sp) results favor the transoid geometry by 1.0 kcal/mol. These barriers of rotation are much smaller than those found by allylidene or formylmethylenephosphorane using the same basis sets.[18] These low barriers are consistent with the NMR data and the discussion in the previous section.

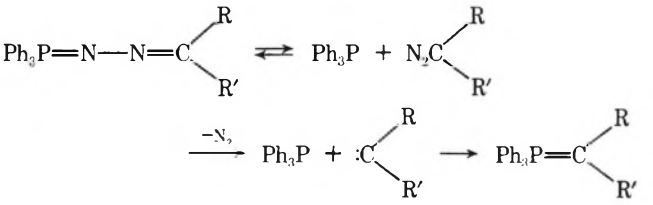
If ^{31}P chemical shifts can be related in a qualitative fashion to the electron density on phosphorus, then the shielding of the ^{31}P chemical shifts of the ylides **1**, **7**, and **9** compared to their respective phosphonium salts[21] is adequately treated by the CNDO/2 (spd) method. It must be emphasized that this technique overestimates the importance of d orbitals.[1,22] However, the fact that the ylides (Table I) are shielded in the ^{31}P NMR from their salts may be partly a consequence of $d_\pi-p_\pi$ overlap.[23] For $H_3P{=}N{-}CH{=}CH_2$ (**17**) and $H_3P{=}N{-}N{=}CH_2$ (**18**) the charges found for phosphorus are essentially identical by CNDO/2 (spd). With CNDO/2 (sp), **18** has greater electron density on phosphorus than that in **17**. Both of these results are not in accord with a comparison of the ^{31}P chemical shifts of **1** and **7**.

Both CNDO/2 methods predict the methylene carbon in $H_3P{=}N{-}CH{=}CH_2$ (**17**) to accommodate some electron density due to delocalization of negative charge from the nitrogen. Rotation of the N–C bond by 90°, however, does not

alter the charge distribution significantly, since the other lone pair on nitrogen can mix almost as effectively with the π orbital of the vinyl group. In **17**, it is found that the charges from phosphorus to the terminal carbon alternate in sign. However, the introduction of an electronegative nitrogen atom β to the phosphorus causes a major redistribution of the electron density in $H_3P{=}N{-}N{=}CH_2$ in **18**. The β nitrogen withdraws electron density in the σ framework from both the α nitrogen and the methylene group, whereas in **17**, a very different situation exists due to the fact that the β atom is carbon. Therefore, CNDO/2 (spd and sp) and Hückel calculations[7b] suggest that there should be significantly less electron density on the methylene carbon in **18** than that in **17**. This is consistent with the ^{13}C chemical shifts of **1**, **2**, **7**, and **8** as discussed in the previous section.

If delocalization of electrons from the α nitrogen to the methylene carbon in **18** were important, then this would serve to decrease the negative charge on the α nitrogen and, thereby, diminish the electrostatic interaction with the positively charged phosphorus. This should serve to weaken the P–N bond, and in fact effects of this type are important for compounds such as **12** and **13** (vide infra). Similar effects have been noted for other highly charged groups.[24]

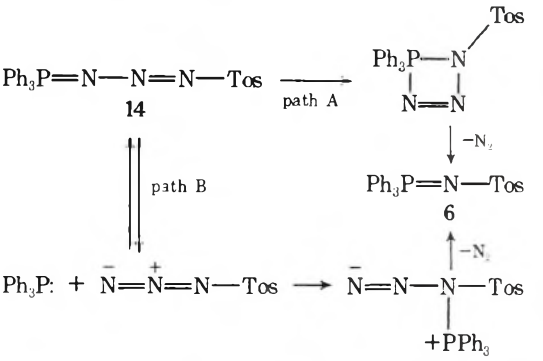
Decomposition of Phosphazines and Phosphazides. The decomposition of a phosphazine to a phosphorane and nitrogen has warranted considerable attention in the literature.[25] The proposed mechanism[25a] for this reaction is as follows:



The evidence for a prior dissociation of the phosphazine to triphenylphosphine and the diazo compound, rather than attack of the methylene carbon on phosphorus and extrusion of nitrogen from the resulting four-center intermediate, is primarily based on the fact that decomposition of a mixture of triphenylphosphine and the diazo compound gives essentially the same product distribution as with the parent phosphazine.[27] We have directly observed the dissociation of phosphazine **12** and **13** by NMR techniques. The ^{31}P NMR spectra of **12** and **13** both show an additional peak at −5.4 ppm, which is assigned to triphenylphosphine. When the temperature in the NMR probe is raised, the peak at −5.4 ppm becomes larger at the expense of the peak attributed to the phosphazine. Cooling the solution restores the original integral ratio of this peak compared to the phosphazine. The addition of triphenylphosphine to solutions of **12** and **13** increases the intensity of the peak at −5.4 ppm, while the addition of the parent diazo compound for **12** and **13** causes it to disappear. Likewise the ^1H NMR spectrum of **13** shows two nonequivalent methoxy resonances for the phosphazine and another single resonance which is identical with that found for authentic dimethyl diazomalonate. This single peak also increases when the temperature is raised at the expense of the two methoxy resonances for **13**.

At 39 °C, a solution of **12** in C_6D_6 contained 7 mol % of triphenylphosphine, based on the total areas of the phosphorus resonances. However, a solution of **13** at the same temperature showed a greater tendency to dissociate as it contained 56 mol % of triphenylphosphine. Similar values, within experimental error, were obtained from the ^1H NMR. No peak for triphenylphosphine was observed when **7** or **9** was heated to 100 °C in benzene or Me_2SO. Therefore, our results indicate that replacement of hydrogen atoms with carbonyl groups on the methylene carbon favors the dissociated products of the phosphazine. This is consistent with the theoretical analysis in the preceding section, in that strong electron withdrawing groups on the methylene carbon will weaken the P–N bond.

N-Tosyltriphenylphosphazide (**14**) and other phosphazides also decompose with loss of nitrogen to form phosphinimines.[4] Two mechanisms can be considered for this reaction:



Path A has been favored by kinetic and nitrogen labeling studies.[27] Our ^{31}P results seem to be in agreement with this since at −10 to 39 °C no triphenylphosphine was observed, although at the latter temperature decomposition of **14** was extremely rapid as evidenced by nitrogen evolution and the increase in intensity of a ^{31}P resonance corresponding to authentic *N*-tosyltriphenylphosphinimine (**6**).

Experimental Section

The phosphinimines, phosphinazines, and phosphonium salts used in this study were prepared by standard routes.[4] The ^{13}C and ^{31}P data were taken at operating frequencies of 22.63 and 36.43 MHz, respectively, on a Bruker HFX-90 spectrometer. All samples were run as 0.1–0.05 M solutions in $CDCl_3$, except **2** in which Me_2SO-d_6 was used as the solvent. Assignment of peaks was accomplished by the use of off-resonance decoupling and model compounds[12] as appropriate.

All calculations were carried out on a Burroughs B6700 computer using the standard CNDO/2 program.

References and Notes

(1) Part 5, in press.
(2) Hercules Inc., Research Center, Wilmington, Del. 19899.
(3) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 619, 635 (1919).
(4) For reviews see G. Singh and H. Zimmer, *Organomet. Chem. Rev.*, **2**, 279 (1967); H. J. Bestmann and R. Zimmerman in "Organic Phosphorus Compounds", Vol. 3, G. M. Kosolapoff and L. Maier, Ed., Wiley-Interscience, New York, N.Y., 1972; A. W. Johnson, "Ylid Chemistry", Academic Press, New York, N.Y., 1966.
(5) See T. A. Albright, W. J. Freeman, and E. E. Schweizer, *J. Am. Chem. Soc.*, **97**, 940 (1975), for a preliminary account of this work.
(6) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970.
(7) W. Buchner and W. Wolfsberger, *Z. Naturforsch. B*, **29**, 328 (1974).
(8) (a) P. Schuster, *Monatsh. Chem.*, **98**, 1311 (1967); (b) H. Goetz and F. Marschner, *Tetrahedron*, **27**, 3581 (1971), and references cited therein.
(9) (a) It is commonly recognized that ^{31}P chemical shifts become shielded by steric compression; see, for example, T. A. Albright, W. J. Freeman, and E. E. Schweizer, *J. Am. Chem. Soc.*, **97**, 2942, 2946 (1975). (b) L. D. Quin and J. J. Breen, *Org. Magn. Reson.*, **5**, 17 (1973); S. I. Featherman, S. O. Lee, and L. D. Quin, *J. Org. Chem.*, **39**, 2899 (1974).
(10) G. A. Gray, *J. Am. Chem. Soc.*, **95**, 7736 (1973).
(11) T. A. Albright, W. J. Freeman, and E. E. Schweizer, *J. Org. Chem.*, **40**, 3437 (1975).
(12) See, for example, J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, especially Chapter 5 and references cited therein.
(13) A similar situation occurs for alkyl- and alkoxycarbonylmethylenephosphoranes. Here the barrier to rotation about the Ph_3PC–C(O)R bond is slow producing different ^{13}C, ^1H, and ^{31}P resonances for the two conformers.[9,14]
(14) D. M. Crouse, A. T. Wehman, and E. E. Schweizer, *Chem. Commun.*, 866 (1968); I. F. Wilson and J. C. Tebby, *J. Chem. Soc., Perkin Trans. 1*, 31 (1972), and references cited therein.
(15) Note that the x-ray structures of the *Z* and *E* conformers in an analogous allylidenetriphenylphosphorane also indicate this; see V. U. Ligner and H. Burzlaff, *Acta Crystallogr., Sect. B*, **30**, 1715 (1974).
(16) S. Evans, J. Kinsel, and E. E. Schweizer, unpublished results.
(17) T. A. Albright, submitted for publication.

(18) A more detailed account of the results of the calculation will be supplied to the reader upon request.
(19) (a) M. J. E. Hewlins, *J. Chem. Soc. B*, 942 (1971); (b) T. S. Cameron, N. J. Hair, and D. G. Morris, *Acta Crystallogr., Sect. B*, **30**, 221 (1974); T. S. Cameron and C. K. Prout, *J. Chem. Soc. C*, 2281, 2285 (1969).
(20) The other bond lengths and angles were taken from standard geometries, since no x-ray data are available.
(21) See B. Ross and K. P. Reetz, *Chem. Ber.*, **107**, 2720 (1974), for analogous data.
(22) See, for example, W. Ensslin, H. Bock, and G. Becker, *J. Am. Chem. Soc.*, **96**, 2757 (1974); S. Rothenberg, R. H. Young, and H. F. Schaefer, III, *ibid.*, **92**, 3243 (1970); M. E. Dyatkina and N. N. Klimento, *Zh. Struct. Khim.*, **14**, 173 (1973).
(23) The shielding in the ^{31}P NMR by $d\pi-p\pi$ overlap has been invoked by several authors; for example, J. C. Williams et al., *Tetrahedron Lett.*, 4749 (1971); H. Goetz, H. Juds, and F. Marschner, *Phosphorus*, **1**, 217 (1972); R. O. Hutchins et al., *J. Am. Chem. Soc.*, **94**, 9151 (1972); B. I. Ionin, *J. Gen. Chem. USSR (Engl. Transl.)*, **38**, 1618 (1968); V. E. Bel'skii et al., *ibid.*, **42**, 2421 (1972); and also see ref 1 and 8a.
(24) M. D. Gordon and J. F. Neumer, *J. Phys. Chem.*, **78**, 1868 (1974); M. Yamakow, *Theor. Chim. Acta*, **15**, 244 (1969).
(25) (a) D. R. Dalton and S. A. Licbman, *Tetrahedron*, **25**, 3321 (1969); D. Seyferth, S. O. Grim, and D. T. Reid, *J. Am. Chem. Soc.*, **83**, 1617 (1961). (b) G. Wittig and K. Schwarzenbach, *Justus Liebigs Ann. Chem.*, **650**, 1 (1961); H. J. Bestmann and L. Gothlich, *ibid.*, **655**, 1 (1962); B. H. Freeman, D. Lloyd, and M. I. C. Singer, *Tetrahedron*, **30**, 211 (1974), and references cited therein.
(26) This should not be taken to imply that the mechanism given above for the decomposition of **7** and **9** is incorrect, since **7** and **9** decompose at temperatures higher than 100 °C.[26a]
(27) J. E. Leffler and R. D. Temple, *J. Am. Chem. Soc.*, **89**, 5235 (1967); H. Bock and M. Schmoller, *Chem. Ber.*, **102**, 38 (1969).
(28) Program 141, Quantum Chemistry Program Exchange, Indiana University.

Quinazolines and 1,4-Benzodiazepines. 74.[1] Phosphorylation[2] of Ambident Anions. Preparation of Some Di-4-morpholinylphosphinyloxy Imines via O-Phosphorylation of Anions of Lactams

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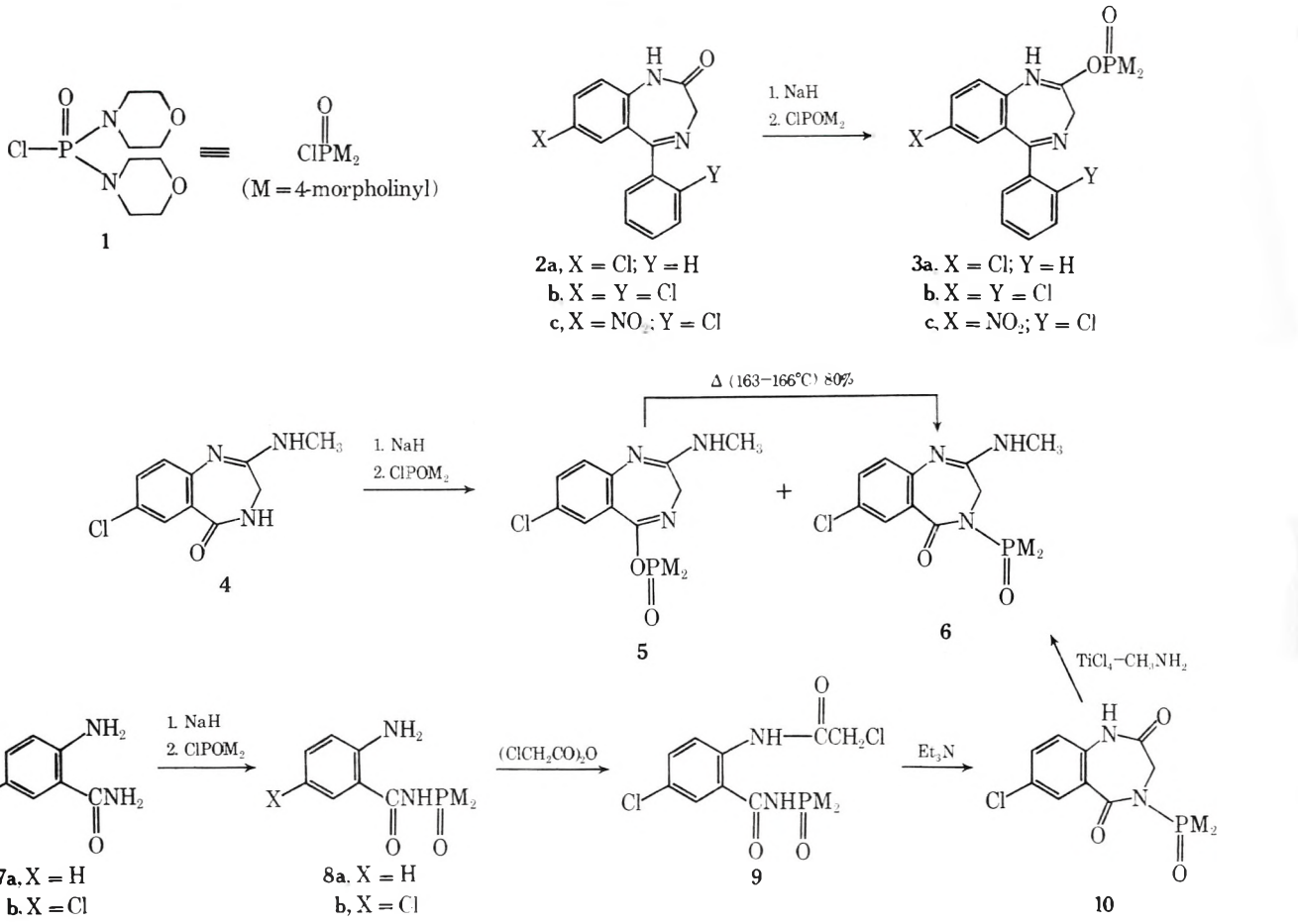
The reaction of ambident anions of amide type with di-4-morpholinylphosphinic chloride (**1**) has been investigated. O-Phosphorylations predominate in the cases of the lactams 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones (**2**), 7-chloro-3,4-dihydro-2-methylamino-5*H*-1,4-benzodiazepin-5-one (**4**), and 2-phenyl-4-quinazolone. The novel dimorpholinylphosphinyloxy imines **3**, **5**, and **11** formed are crystalline and readily isolable. In contrast, reaction of **1** with the anions of anthranilamides **7**, 8-chloro-2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one, 2-hydroxybenzimidazole, and 2-benzoxazolinone afforded good yields of the N-phosphorylated products **8**, **13**, **14**, and **15**, respectively. A thermal isomerization of the O-phosphorylated compound **5** to the N-phosphorylated isomer **6** is also observed. Compound **6** was prepared independently from the anthranilamide derivative **8**.

Although the reaction of phosphorylating agents[3–5] with enolate anions[6,7] has been studied extensively, there is a paucity of information on the reaction of these agents with ambident anions containing nitrogen and oxygen sites. Enolate anions phosphorylate almost exclusively on oxygen. In contrast, the site of phosphorylation of nitrogen-containing ambident anions seems less predictable. 2-Hydroxypyridine and 4-hydroxypyridine with phosphoryl chloride in aqueous alkali were reported to yield *O*-phosphoryl and *N*-phosphoryl derivatives, respectively.[8]

We now wish to report the results of some investigations carried out on the ambident anions of amides using di-4-morpholinylphosphinic chloride (**1**)[9,10] as the phosphorylating agent. Compound **1** is a crystalline (mp 80–82 °C) and readily available[14] reagent useful in the preparation of phosphate monoesters.[9a,15] Both O-phosphorylation and N-phosphorylation reactions were observed, with selectivity depending on the amide used. The preference for the oxygen site of the anions of cyclic secondary amides has permitted the isolation, in good yields, of the novel[11] and synthetically useful[13] dimorpholinylphosphinyloxy imines **3** and **5** in the 1,4-benzodiazepine series. When a slight excess of **1** was allowed to react with anions derived from 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (**2**) in tetrahydrofuran at room temperature, the predominant products formed, as evident by TLC, were the O-phosphorylated products **3**, which could be isolated in 43–66% yields. Although crystalline and readily isolable, these dimorpholinyloxy imines are quite reactive toward nucleophiles to give 2-substituted benzodiazepines.[13] The infrared spectra of **3** indicate the absence of lactam carbonyl signals (typically strong bands at about 1680 cm^{-1}). When 7-chloro-3,4-dihydro-2-methylamino-5*H*-1,4-benzodiazepin-5-one[16] compound **4** was treated with sodium hydride followed by **1**, the O-phosphorylated product **5** crystallized in 48% yield. The N-phosphorylated product **6** was eventually also isolated (9% yield) from the same reaction mixture. However, owing to the complexity of the mixture, this isolation was not achieved until a reference sample of **6** was synthesized from compound **8b** by an alternate process as described below. In contrast to the cyclic amides **2** and **5**, it was found that the anthranilamides **7**, under the same conditions, afforded the N-phosphorylated products **8** in yields of 58–62%. Chloroacetylation of 2-amino-5-chloro-*N*-(di-4-morpholinylphosphinyl)benzamide (**8b**) led to the chloroacetanilide **9** (95%) which was cyclized in the presence of triethylamine to 7-chloro-4-(di-4-morpholinyl)phosphinyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-2,5-dione (**10**, 65%). The *N*-dimorpholinylphosphinylamide group in **10** survived a titanium tetrachloride–methylamine treatment[17] leading to the amidine **6** in 57% yield. While compound **6** was relatively thermally stable (as a melt at 220 °C for 2 min), the O-phosphorylated isomer compound **5** was not. In refluxing mesitylene (bp 163–166 °C), **5** isomerized in 80% yield, to the N isomer **6**. This observation suggests that the predominance of O-phosphorylation leading to **3** and **5** is kinetic in nature, and that N-phosphorylation is thermodynamically preferred.

To extend our observations to ambident anions of aromatic cyclic amide, cyclic urea, and cyclic carbamate types, we chose the following compounds purely on the basis of their potential usefulness as intermediates leading to new derivatives of potential medicinal utility: 2-phenyl-4-quinazolone,[18] 3-amino-6-chloro-4-phenylcarbostyril,[19] 8-chloro-2,4-dihy-



1

2a, X = Cl; Y = H
b. X = Y = Cl
c, X = NO_2; Y = Cl

3a. X = Cl; Y = H
b. X = Y = Cl
c, X = NO_2; Y = Cl

4

5

6

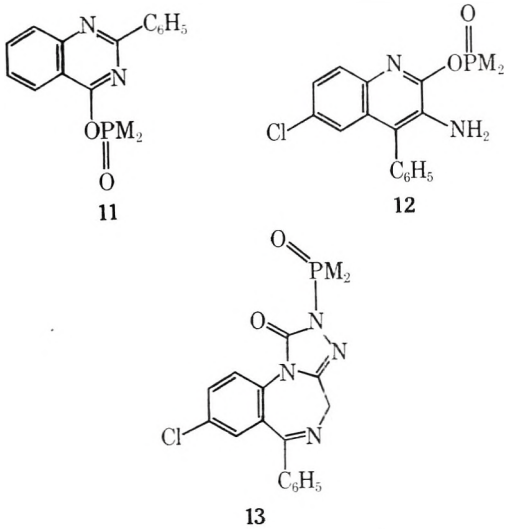
7a, X = H
b. X = Cl

8a. X = H
b, X = Cl

9

10

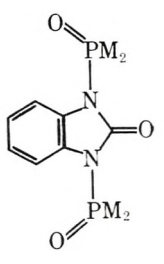
dro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one,[20] 2-hydroxybenzimidazole, and 2-benzoxazoline. The anions, which were generated with sodium hydride, were treated with di-4-morpholinylphosphinic chloride (1) as before. In each case, only one crystalline product was isolated: compounds **11** (77%), **12** (33%), **13** (72%), **14** (42%), and **15** (42%), respectively. The structures were assigned on the basis of the presence or the absence of the carbonyl absorption band in the infrared spectra, and were further corroborated by NMR, uv, and mass spectral data. Owing to the complexity of the reaction product mixtures, no other products were isolated. In the cases where only the products of N-phosphorylation were isolated (**13, 14,** and **15**), we did not expend any great effort in an attempt to isolate the corresponding O-phosphorylated products. Since there is no reason to doubt that these compounds are formed we suspect that they are too unstable to survive the reaction conditions and isolation procedures. The relatively good yields of **13, 14,** and **15** may reflect not only their formation in the primary step, but also their formation in secondary reactions involving the more reactive O-phosphorylated intermediates. Both O to N isomerizations, as observed in the conversion of **5** to **6**, and intermolecular phosphoryl transfer[12] involving unreacted starting anions are possible.



11

12

13



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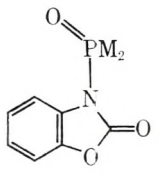

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An extension of these observations to other ambident anions as well as the synthetic utility of both the O- and N-phosphorylated products is currently being investigated.

Experimental Section

All melting points were taken in capillaries heated in oil baths, and are corrected. Infrared spectra were determined on a Beckman IR-9 or a Perkin-Elmer 621 grating spectrometer, mass spectra on a Jeolco O1SG or a CEC-21-110 spectrometer, nuclear magnetic resonance spectra on a Varian A-30 or a Varian HA-100 spectrometer, using tetramethylsilane as internal standard, and ultraviolet spectra with a Cary 14M or 15 recording spectrometer. Solvents used were of reagent grade purity. Petroleum ether used boils at 30–60 °C. Tetrahydrofuran and dimethylformamide were dried by passage over activity 1 alumina or molecular sieves. Unless otherwise specified, all solvents were evaporated on a Büchi Rotavapor evaporator under water-aspirator pressure using a water bath set at 40–70 °C.

The progress of reactions was routinely followed by thin layer chromatography (TLC). The TLC was performed on glass plates

coated with Mallinckrodt Silica 7GF5 (with fluorescent indicator) in the case of analytical TLC and Merck silica gel PF254 in the case of preparative TLC. All plates were activated by heating to 100 °C for 1 h, then stored at 20–50 °C. The chromatograms were developed over a distance of 10 cm, then viewed or photographed under uv light.

Di-4-morpholinylphosphinic Chloride (1).[9,10] A solution of 95 ml (1.03 mol) of phosphorus oxychloride in 1000 ml of benzene in a dry 3-l., three-necked flask fitted with a stirrer, a thermometer, and a dropping funnel mounted on an adaptor with a small vent for escaping HCl was chilled in an ice bath to 5 °C. To the chilled mixture was added, dropwise over 1.5 h, 355 g (4.075 mol) of morpholine keeping the temperature between 10 and 20 °C by regulating the rate of addition. After addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. Insoluble, colorless salts which formed were collected in a sintered glass funnel and washed thoroughly three times with 800-ml portions of benzene. The combined filtrate and washings were evaporated to dryness. The residue was dissolved by heating (steam bath) in 300 ml of benzene. The hot benzene solution was filtered to remove an insoluble gum (about 5 g) and diluted with 200 ml of cyclohexane. If dilution at this point causes a small amount of precipitation, this should be removed by filtration before further dilution. The mixture should be kept warm throughout this process. The mixture was further diluted with 700 ml of cyclohexane and the product allowed to crystallize at room temperature. The colorless prisms were collected with minimal exposure to moist air, and washed with two 500-ml portions of petroleum ether. It weighed 205.5 g, mp 79–81 °C. Concentration of the mother liquors yielded a second crop of colorless prisms, 26.5 g, mp 77–79 °C. The total yield was 232 g (91%). This material was dried under high vacuum (avoid water aspirators) at 40–50 °C and was used without recrystallization. Recrystallizations did not appreciably raise the melting point. An analytical sample melted at 80–82 °C (lit.[9] mp 81 and 76–80 °C); ir (KBr) 1238 cm^{-1} (P=O).

Stability and Handling of 1. Although 1 has been used conveniently and successfully without dryboxes, its instability is obvious. Crystals kept in open dishes on dry days turned to puddles within 2 days. Several batches of this reagent, kept without special precautions in brown glass screw-cap bottles, developed elevated melting points and wider melting ranges even though there was little change in the fluidity of the solids. Although the pure reagent is entirely soluble in warm benzene in the concentration of 2 g per 5 ml of benzene, partly degenerated samples contained considerable amounts of benzene-insoluble materials, which could be due to the salts of morpholine which results from the hydrolysis of the reagent. On this basis, we recommend that the reagent be handled and stored as much as possible under argon. The purity of the material could be tested by determination of melting point (both elevation and depression of melting point from 79–81 °C indicate impurity) and solubility in benzene (2 g per 5 ml of hot benzene). Partially decomposed materials may be recrystallized by the following procedure. The solid was dissolved by gentle heating in benzene (5 ml per 2 g). The insoluble material was removed by filtration. To the warm benzene filtrate was added 1.5 volumes of cyclohexane. The mixture was allowed to crystallize in a stoppered flask. The crystals (colorless prisms) were collected with minimum exposure to air, washed with cyclohexane and then petroleum ether, and dried under high vacuum.

General Procedure for Phosphorylations with Di-4-morpholinylphosphinic Chloride in the Preparations of 3a–c, 5, 6, 8a,b, 11, 12, 13, and 15. To a stirred solution (suspension in the case of 5) of the amide in dry tetrahydrofuran (2–15 ml/mmol; dimethylformamide was used in the case of 12) was added a 50% dispersion of sodium hydride in mineral oil (1.1–2.0 equiv of hydride). The mixture was stirred at room temperature under nitrogen until hydrogen evolution ceased (0.5–1 h). Di-4-morpholinylphosphinic chloride (1, 1.2–2.0 equiv relative to the amide) was added in one portion (at 0–25 °C). The mixture was stirred at room temperature for 2–4 h. Insoluble salts were removed by filtration. Solvent was evaporated. Crystallization of the residue from an appropriate solvent afforded the products.

7-Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3*H*-1,4-benzodiazepine (3a). From 5.4 g (20 mmol) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one[21] (2a), following the general phosphorylation procedure, the product (4.2 g, 43%, mp 189–191 °C) was obtained by crystallization from ethyl acetate. Recrystallization from methylene chloride–ether–petroleum ether afforded colorless prisms: mp 184–186 °C; ir (KBr) 1660 (medium, O–C=N) and 1255 cm^{-1} (P=O); uv max (2-PrOH) 217 nm (ϵ 34 700), 255 (sh 14 300), and 317 (2060); mass spectrum *m/e* 488 (M^+).

Anal. Calcd for $C_{23}H_{26}ClN_4O_4P$: C, 56.50; H, 5.36; N, 11.46. Found: C, 56.30; H, 5.30; N, 11.40.

7-Chloro-5-(2-chlorophenyl)-2-(di-4-morpholinylphosphinyloxy)-3*H*-1,4-benzodiazepine (3b).[22] From 122 g (0.40 mol) of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one[21] (2b), following the general procedure, the product (140 g, 66%, mp 180–183 °C) was obtained by crystallization from ethyl acetate. Recrystallization from methylene chloride–ether afforded colorless needles: mp 185–187 °C; ir (KBr) 1660 (medium, O–C=N) and 1255 cm^{-1} (P=O); uv max (CH_3CN) 216 nm (δ 41 500), 270 (sh, 8000), and 315 (2100); mass spectrum *m/e* 522 (M^+).

Anal. Calcd for $C_{23}H_{25}Cl_2N_4O_4P$: C, 52.78; H, 4.81; N, 10.71. Found: C, 52.95; H, 4.99; N, 10.81.

5-(2-Chlorophenyl)-2-(di-4-morpholinylphosphinyloxy)-7-nitro-3*H*-1,4-benzodiazepine (3c). From 4.74 g (15 mmol) of 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one[21] (2c), following the general procedure, the product (3.75 g, 47%, mp 214–216 °C) was obtained as colorless needles by crystallization from methylene chloride–ether: ir (KBr) 1660 (medium, O–C=N) and 1255 cm^{-1} (P=O); uv max (CH_3CN) 215 nm (sh, ϵ 30 800), 245 (sh 17 300), and 313 (11 250); mass spectrum *m/e* 533 (M^+).

Anal. Calcd for $C_{23}H_{25}ClN_5O_5P$: C, 51.74; H, 4.72; N, 13.12. Found: C, 51.90; H, 4.70; N, 13.11.

7-Chloro-5-(di-4-morpholinyl)phosphinyloxy-2-methylamino-3*H*-1,4-benzodiazepine (5). From 22 g (0.10 mol) of 7-chloro-3,4-dihydro-2-methylamino-5*H*-1,4-benzodiazepin-5-one (4),[16] following the general procedure above, 5 crystallized from ethyl acetate as 20.8 g (47%) of colorless prisms, mp 195–196 °C.

An analytical sample was prepared by recrystallizations from ethyl acetate to yield colorless prisms: mp 210–212 °C; ir (KBr) 1190 and 1240 cm^{-1} (P=O); mass spectrum *m/e* 441 (M^+), 206 (M − dimorpholinylphosphinyloxy).

Anal. Calcd for $C_{18}H_{25}ClN_5O_4P$: C, 48.93; H, 5.70; N, 15.84. Found: C, 49.17; H, 5.77; N, 15.87.

7-Chloro-3,4-dihydro-4-(di-4-morpholinylphosphinyl)-2-methylamino-5*H*-1,4-benzodiazepin-5-one (6). A. From Phosphorylation of Amide. The experiment described for the preparation of 5 was conducted on 1.0-mmol scale (223 mg, 4). The O-phosphorylated product 5 (R_f 0.40, silica gel, 1:1 EtOH–EtOAc; mp 209–211 °C) was obtained as before by crystallization from ethyl acetate in 48% yield (210 mg). The product mixture in the mother liquor was separated by preparative TLC (silica gel, 1:1 EtOH–EtOAc). The N-phosphorylated product 6 (R_f 0.30) was isolated, using ethanol for desorption from silica gel. Crystallization from acetonitrile afforded 40 mg (9%) of 6, mp 236–238 °C, identical (TLC, mixture melting point) with reference 6 prepared by method B.

B. From 10. To a stirred solution of 429 mg (1.00 mmol) of 10 in 10 ml of a 3.8 M solution of methylamine in tetrahydrofuran at room temperature was added a solution of 0.18 ml (1.5 mmol) of titanium tetrachloride in 3 ml of benzene. The resulting mixture was kept at room temperature for 2 days. About 2 ml of water was added and the insoluble salts were removed by filtration. Tetrahydrofuran was evaporated. The residue was partitioned between water and methylene chloride. The organic layer was dried and evaporated. Crystallization of the residue from ethyl acetate–hexane gave 258 mg (57%) of the desired product. An analysis sample was prepared by recrystallization from acetonitrile. Colorless prisms were obtained: mp 233–235 °C; ir (KBr) 3265 and 3110 (NH), 1650 (C=O), and 1260 and 1220 cm^{-1} (P=O); uv max (CH_3CN) 227 nm (ϵ 22 190), 274 (15 800), and 333 (4250); mass spectrum *m/e* 441 (M^+); NMR ($CDCl_3$) δ 2.93 (d, 3, CH_3), 3.18 (broad, 8, NCH_2 of morpholines), 3.61 (broad, 8, OCH_2 of morpholines), 3.9 and 4.4 (broad, 2, CH_2), 5.70 (broad, 1, NH), 7.06 (d, J_o = 9 Hz, 1, H-9), 7.35 (dd, J_o = 9, J_m = 2.5 Hz, 1, H-8), and 7.75 ppm (d, 1, H-6).

Anal. Calcd for $C_{18}H_{25}ClN_5O_4P$: C, 48.93; H, 5.70; N, 15.85. Found: C, 49.16; H, 5.70; N, 16.12.

C. By Thermal Isomerization of 5. A suspension of 442 mg (1.0 mmol) of 5 in 5 ml of mesitylene (bp 163–166 °C) was heated to reflux for 2 h. The solids dissolved before precipitation of the isomerized product: 345 mg (80%), mp 228–230 °C; identical with 6 obtained from B by TLC and comparison of infrared spectra.

The N-phosphorylated product 6 is relatively stable thermally. It remained essentially unchanged (TLC) after heating as a melt at 220 °C for 2 min or in refluxing solution in dimethylformamide.

2-Amino-*N*-(di-4-morpholinylphosphinyl)benzamide (8a). Following the general phosphorylation procedure described above. 81.6 g (0.60 mol) of anthranilamide (Aldrich) afforded a dry product mixture which was shaken with aqueous sodium bicarbonate and methylene chloride. The colorless product crystallized from the two-phase mixture and was collected and washed with water followed

by a mixture of methylene chloride and petroleum ether. It weighed 131 g (62%), mp 216–218 °C. On recrystallization from methylene chloride–ether, colorless needles were obtained: mp 215–217 °C; ir (KBr) 3460 and 3340 (NH_2), 3160 (NH), 1670 (C=O), and 1260 and 1190 cm^{-1} (P=O); uv max (CH_3CN) 219 nm (ϵ 26 500), 250 (7850), and 338 (5190); (1.0 N HCl) 230 nm (ϵ 11 750) and 270 (shoulder, 1740); NMR ($CDCl_3$) δ 5.84 (s, 2, NH_2) and 7.91 ppm (d, 1, NH).

2-Amino-5-chloro-*N*-(di-4-morpholinylphosphinyl)benzamide (8b). Starting with 0.5 mol of 2-amino-5-chlorobenzamide[23] (mp 169–171 °C, needles from ethanol, prepared from commercial 5-chloroisatoic anhydride by heating in 1 M aqueous ammonia), and following the same procedure described above for the dechloro analogue **8a**, the colorless product **8b** was isolated in the same manner in 58% yield, mp 223–225 °C. Recrystallization from ethanol afforded prisms: mp 218–220 °C; ir (KBr) 3460 and 3320 (NH_2), 3180 (NH), 1670 (C=O), and 1255 and 1180 cm^{-1} (P=O); uv max ($CHCl_3$) 239 nm (ϵ 7290), 249 (8820), and 354 (4920); NMR ($CDCl_3$) δ 3.27 (m, 8, NCH_2 of morpholines), 3.65 (m, 8, OCH_2 of morpholines), 5.80 (s, 2, NH_2) 6.60 (d, J = 9 Hz, 1 aromatic H-3), 7.18 (dd, J = 9 and 2.5 Hz, 1, aromatic H-4), 7.95 (d, J = 2.5 Hz, 1 aromatic H-6), and 8.85 ppm (d, 1, NH).

Anal. Calcd for $C_{15}H_{22}ClN_4O_4P$: C, 46.34; H, 5.70; N, 14.41. Found: C, 46.46; H, 5.71; N, 14.28.

5-Chloro-2-(2-chloroacetylamino)-*N*-(di-4-morpholinylphosphinyl)benzamide (9). A mixture of 54.5 g (140 mmol) of **8b** and 72 g (420 mmol) of chloroacetic anhydride was stirred in 250 ml of benzene at room temperature overnight. Approximately 1200 ml of aqueous sodium bicarbonate (0.8 M) was added and the two-phase mixture was stirred vigorously until all bubbling stopped. The solids which precipitated were collected and washed with water to give 61.5 g (95%) of the desired product, mp 212–214 °C dec. An analysis sample was prepared by recrystallization from methylene chloride–hexane to give colorless prisms: mp 215–216 °C dec; ir (KBr) 1690 and 1665 (two C=O) and 1260 and 1200 cm^{-1} (P=O); uv max (2-PrOH) 223 nm (ϵ 24 000), 257 (14 600), and 312 (3800); NMR (DMF-d_7) 3.26 (m, 8, NCH_2 of morpholines) 3.65 (m, 8, OCH_2 of morpholines), 4.47 (s, 2, CH_2), 7.67 (dd, J = 2.5 and 9.0 Hz, 1, aromatic H-4), 8.08 (d, 1, J = 2.5 Hz, aromatic H-6), 8.40 (d, J = 9.0 Hz, 1, aromatic H-3), 9.82 (broad, 1, NH), and 11.31 ppm (broad, 1, NH).

Anal. Calcd for $C_{17}H_{23}Cl_2N_4O_5P$: C, 43.89; H, 4.98; N, 12.04; Cl, 15.24. Found: C, 43.85; H, 4.97; N, 12.17; Cl, 15.28.

7-Chloro-4-(di-4-morpholinyl)phosphinyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine-2,5-dione (10). A mixture of 2.3 g (5.0 mmol) of **9** in 40 ml of methanol containing 5 ml of triethylamine was heated to reflux for 3 h. Methanol was evaporated. The residue was partitioned between water and methylene chloride. The organic layer was dried and evaporated. Crystallization of the residue from ethanol yielded 1.4 g (65%) of the desired product, mp 213–215 °C. An analysis sample was prepared by recrystallization from ethanol to give colorless prisms: mp 216–218 °C; ir (KBr) 1700 and 1658 (two C=O) and 1260 and 1210 cm^{-1} (P=O); uv max (EtOH) 220 nm (ϵ 35 500), 250 (13 800), and 310 (2800); NMR ($CDCl_3$) δ 3.23 (m, 8, NCH_2 of morpholines), 3.65 (m, 8, OCH_2 of morpholines), 4.35 (d, J_{H-P} = 9.0 Hz, 2, CH_2), 7.13 (d, J = 9.0 Hz, 1, H-9), 7.48 (dd, J = 2.5 and 9.0 Hz, 1, H-8), 7.86 (d, J = 2.5 Hz, 1, H-6), and 9.57 ppm (s, 1, NH).

Anal. Calcd for $C_{17}H_{22}ClN_4O_5P$: C, 47.62; H, 5.17; N, 13.07. Found: C, 47.57; H, 5.09; N, 13.36.

4-(Di-4-morpholinylphosphinyloxy)-2-phenylquinazoline (11). Phosphorylation of 33.4 g (150 mmol) of 2-phenyl-4-quinazolone[18] using the general procedure described above afforded a mixture which crystallized from ethyl acetate to give 50.8 g (77%) of the desired product, mp 153–155 °C. Recrystallization from ethyl acetate–ether afforded colorless prisms: mp 152–154 °C; ir (KBr) no carbonyl band (1600–1800 cm^{-1}); 1250 cm^{-1} (P=O); uv max (2-PrOH) 207 nm (ϵ 40 500), 255 (sh, 33 800), 259 (35 000), 285 (16 500), and 330 (sh, 2550); mass spectrum m/e 440 (M^+).

Anal. Calcd for $C_{22}H_{25}N_4O_4P$: C, 60.00; H, 5.73; N, 12.72. Found: C, 59.93; H, 5.71; N, 12.62.

3-Amino-6-chloro-2-(di-4-morpholinyl)phosphinyloxy-4-phenylquinoline (12). A solution of 2.7 g (10 mmol) of 3-amino-6-chloro-4-phenylcarbostyril[19] in 40 ml of dry dimethylformamide was treated in the manner described in the general procedure. The residue from the evaporation of dimethylformamide, on trituration with ether, gave 1.6 g (33%) of a light brown amorphous solid, mp 185–187 °C.

An analytical sample was prepared by recrystallization from ethyl acetate to yield buff prisms: mp 188–190 °C; ir (KBr) 1220 and 1250 cm^{-1} (P=O), no carbonyl band; uv max (2-PrOH) 249 nm (ϵ 42 100) and 344 (8600).

Anal. Calcd for $C_{23}H_{26}ClN_4O_4P$: C, 56.50; H, 5.36; N, 11.45. Found: C, 56.43; H, 5.21; N, 11.40.

8-Chloro-2,4-dihydro-2-(di-4-morpholinyl)phosphinyl-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one (13). From 621 mg (2 mmol) of 8-chloro-2,3-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one[20] (mp 251–253 °C with correct C, H, N elemental analyses) following the general phosphorylation procedure and crystallization from ether, 770 mg (72%) of **13** was obtained, mp 172–175 °C. Recrystallizations from ethyl acetate–ether afforded colorless, amorphous solids: mp 179–181 °C; ir (KBr) 1720 (C=O) and 1240 cm^{-1} (P=O); uv max (CH_3CN) 208 nm (ϵ 41 200), 245 (20 000), and 306 (700), almost identical with that of starting material.

Anal. Calcd for $C_{24}H_{26}ClN_6O_4P$: C, 54.50; H, 4.95; N, 15.89. Found: C, 54.37; H, 4.73; N, 16.08.

1,3-Bis[(di-4-morpholinyl)phosphinyl]benzimidazol-2-one (14). To a stirred solution of 10.7 g (80 mmol) of 2-hydroxybenzimidazole (Aldrich Chemical Co.) in 150 ml of dry dimethylformamide at room temperature was added 7.7 g of a 50% dispersion of sodium hydride in oil (160 mmol of hydride). The thick mixture was stirred at room temperature for 1.5 h until hydrogen evolution stopped. The mixture was then chilled in a dry ice–acetone bath and 44.8 g (176 mmol) of di-4-morpholinylphosphinic chloride was added in portions. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. Dimethylformamide was evaporated and the residue was slurried with methylene chloride. Insoluble salts were removed by filtration and methylene chloride was evaporated. Crystallizations of the residue from ethanol gave 19.1 g (42%) of colorless flakes: mp 214–217 °C; ir (KBr) 1710 cm^{-1} (C=O); NMR indicated a symmetrical molecule; mass spectrum m/e 570 (M^+).

Anal. Calcd for $C_{23}H_{36}N_6O_7P_2$: C, 48.42; H, 6.36; N, 14.73. Found: C, 48.70; H, 6.14; N, 14.60.

3-(Di-4-morpholinylphosphinyl)benzoxazolin-2-one (15). Phosphorylation of 1.00 g (7.4 mmol) of 2-benzoxazolinone (Aldrich Chemical Co.) following the general procedure, then crystallization from ether afforded 1.5 g of **15** as a colorless, amorphous solid, mp 143–145 °C. Recrystallization from ethanol afforded 1.1 g (42%) of colorless prisms, mp 148–150 °C (repeated recrystallizations raised the melting point to 152–153 °C); ir (KBr) 1785 cm^{-1} (C=O); mass spectrum m/e 353 (M^+).

Anal. Calcd for $C_{15}H_{20}N_3O_5P$: C, 50.99; H, 5.71; N, 11.89. Found: C, 50.98; H, 5.67; N, 11.80.

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Registry No.—**1**, 7264-90-6; **2a**, 1088-11-5; **2b**, 2894-67-9; **2c**, 1622-61-3; **3a**, 59318-11-5; **3b**, 59349-85-8; **3c**, 59349-86-9; **4**, 33544-57-9; **5**, 59318-14-8; **6**, 59349-87-0; **7a**, 88-68-6; **7b**, 5202-85-7; **8a**, 59349-88-1; **8b**, 59349-89-2; **9**, 59349-90-5; **10**, 59349-91-5; **11**, 59349-92-7; **12**, 59318-12-6; **13**, 59349-93-8; **14**, 59349-94-9; **15**, 59349-95-0; phosphorus oxychloride, 13779-42-5; morpholine, 110-91-8; chloracetic anhydride, 541-88-8; 2-phenyl-4-quinazolone 1022-45-3; 3-amino-6-chloro-4-phenylcarbostyril, 5220-83-7; dimethylformamide, 68-12-2; 8-chloro-2,3-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one, 59349-96-1; 2-hydroxybenzimidazole, 5400-74-8; benzoxazolinone, 59-49-4.

References and Notes

(1) Part 73: R. I. Fryer, J. V. Earley, N. W. Gilman, and W. Zally, *J. Heterocycl. Chem.*, in press.
(2) Throughout this paper, the term "phosphorylating" is used in its broadest sense. It refers to the process of the introduction of a XYP=O group in which X and Y are substituents bonded to phosphorus through a heteroatom, such as halogen, oxygen, and nitrogen atoms.
(3) D. M. Brown, *Adv. Org. Chem.*, **3**, 75 (1963).
(4) V. M. Clark, D. W. Hutchinson, A. J. Kirby, and S. G. Warren, *Angew. Chem., Int. Ed. Engl.*, **3**, 678 (1964).
(5) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, 2, and 4, Wiley, New York, N.Y., 1967, 1969, and 1974.
(6) (a) H. Kolind-Andersen and S. O. Lawesson, *Acta Chem. Scand., Ser. B*, **29**, 430 (1975), and references cited therein. (b) R. E. Ireland, D. C. Muchmore, and U. Hengartner, *J. Am. Chem. Soc.*, **94**, 5098 (1972); I. J. Borowitz, S. Firstenberg, E. W. R. Casper, and R. K. Crouch, *J. Org. Chem.*, **36**, 3282 (1971).
(7) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961).
(8) E. Guibe-Jampel and M. Wakselman, *Chem. Commun.*, 720 (1969).
(9) (a) H. A. C. Montgomery and J. H. Turnbull, *J. Chem. Soc. C*, 1963 (1958); (b) R. J. W. Cremlyn, B. B. Dewhurst, and D. H. Wakeford, *ibid.*, 300 (1971).
(10) This reagent has been called dimorpholinophosphorochloridate (ref 9) and phosphorodimorpholidic chloride (ref 5). The name used here is that found

in the indexes of *Chemical Abstracts* (a recent entry: **80**, 1974).
(11) Dimorpholinylphosphinyloxy imines are stabilized analogues of the corresponding phosphates, the imidoylphosphates, a class of widely postulated reaction intermediates which have never been isolated (ref 4 and 12).
(12) V. M. Clark and D. W. Hutchinson, *Prog. Org. Chem.*, **7**, 75 (1968).
(13) R. Y. Ning, R. I. Fryer, P. B. Madan, and B. C. Sluboski, *J. Org. Chem.*, following paper in this issue.
(14) A modified procedure used in kilogram-scale preparation of this reagent along with some handling and storage characteristics of **1** are included in the Experimental Section.
(15) (a) K. Irmscher, *Chem. Ind. (London)*, 1035 (1961); (b) G. C. K. Roberts, J. Hannah, and O. Jardetzky, *Science*, **165**, 504 (1969); (c) K. Sempuku, *Chem. Pharm. Bull.*, **21**, 437 (1973).
(16) G. F. Field, L. H. Sternbach, and W. J. Zally, Swiss Patent 503 040 (March 31, 1971); *Chem. Abstr.*, **75**, P110344w (1971).
(17) R. I. Fryer, J. V. Earley, G. F. Field, W. Zally, and L. H. Sternbach, *J. Org. Chem.*, **34**, 1143 (1969).
(18) This is a known compound: H. Stephen and G. Wadge, *J. Chem. Soc.*, 4420 (1956). We prepared it by benzoylation of commercial anthranilamide, followed by cyclization as described by Stephen and Wadge above.
(19) R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3097 (1964).
(20) J. B. Hester, Jr., D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1609 (1971): mp 255–256 °C.
(21) These lactams (**2a–d**) are intermediates in the syntheses of benzodiazepines of clinical importance: L. O. Randall, W. Schallek, L. H. Sternbach, and R. Y. Ning in "Psychopharmacological Agents", Vol. III, M. Gordon, Ed., Academic Press, New York, N.Y., 1974, pp 175–281.
(22) This experiment was conducted in the laboratory of Dr. A. Walser.
(23) N. D. Heindel, W. P. Fives, T. F. Lemke, and R. A. Carrano, *J. Pharm. Sci.*, 60, 703 (1971): mp 170–172 °C.

Quinazolines and 1,4-Benzodiazepines. 76[1]. Reactions of Some Di-4-morpholinylphosphinyloxy Imines

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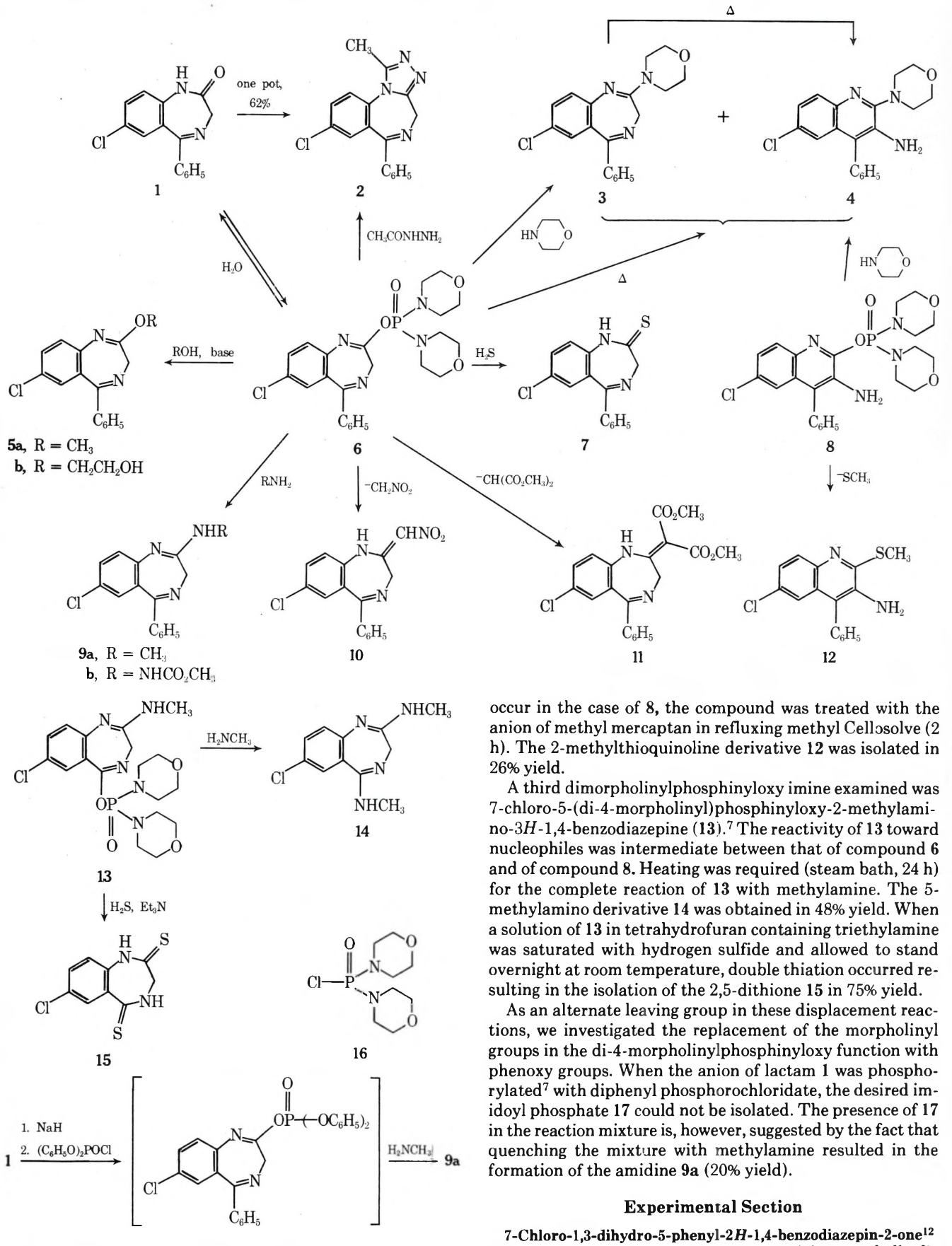
The reaction of 7-chloro-2-(di-4-morpholinyl)phosphinyloxy-5-phenyl-3*H*-1,4-benzodiazepine (**6**), 7-chloro-5-(di-4-morpholinyl)phosphinyloxy-2-methylamino-3*H*-1,4-benzodiazepine (**13**), and 3-amino-6-chloro-2-(di-4-morpholinyl)phosphinyloxy-4-phenylquinoline (**8**) with a variety of nucleophiles illustrates the imidoyl character of the dimorpholinylphosphinyloxy imines. Of particular interest is the facile reaction of **6** with amines, alcohols, hydrogen sulfide, and carbanions to give the corresponding 2-substituted benzodiazepines. Pyrolysis of **6** in refluxing trichlorobenzene afforded a mixture of 7-chloro-2-(4-morpholinyl)-5-phenyl-3*H*-1,4-benzodiazepine (**3**) and 3-amino-6-chloro-2-(4-morpholinyl)-4-phenylquinoline (**4**). Compound **3** under the same conditions was shown to isomerize to **4**.

The chemical activation of secondary amides via transformations to imidates,[2] imidoyl halides,[2] thioamides,[3] amidines,[2c,4] and *N*-nitrosoamidines,[5] among others, have imparted great synthetic utility to these amides as intermediates. We have recently reported that medicinally interesting cyclic secondary amides in the 1,4-benzodiazepine[6] series can be derivatized by O-phosphorylation under *mild, basic* conditions.[7] Phosphorylation of the ambident amide anions with dimorpholinylphosphinic chloride (**16**) afforded the novel dimorpholinylphosphinyloxy imines such as **6** and **13** which were isolated in good yields. In this paper, we describe reactions of some of these dimorpholinylphosphinyloxy imines which point to their versatility as intermediates.[8] These intermediates offer a valuable alternate to other imidoyl compounds which are often difficult to generate in sensitive molecules.

7-Chloro-2-(di-4-morpholinylphosphinyloxy)-5-phenyl-3*H*-1,4-benzodiazepine (**6**)[7] reacts with a variety of nucleophiles to give various 2-substituted benzodiazepines through displacement of the dimorpholinylphosphinyloxy group. Exposure of **6** to methanol containing sodium methoxide and to ethylene glycol containing triethylamine afforded the corresponding 2-alkoxy derivatives **5a** and **5b** in 87 and 82% yields, respectively. The displacement reaction is nearly instantaneous at room temperature with hydrogen sulfide–triethylamine, methylamine, and methyl hydrazinocarboxylate, giving **7** (78%), **9a** (96%), and **9b** (84%), respectively. Of particular interest is the carbon–carbon bond formation through the displacement of the dimorpholinylphosphinyloxy group with carbanions. We have found (conditions not optimized) that the reaction of **6** with the anions of nitromethane and dimethyl malonate afforded 7-chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2*H*-1,4-benzodiazepine (**10**, 27%)[9] and 7-chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2*H*-1,4-benzodiazepine (**11**, 13%),[5] respectively. The utility of **6** as an intermediate has been further demonstrated by its facile conversion (80%) to 1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**2**),[3c,10] a benzodiazepine of clinical interest.[6] We have also found that compound **2** can be prepared in a simple procedure by reacting 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**1**) with sodium hydride, di-4-morpholinylphosphinic chloride,[7] and acetylhydrazide, in that order, in the same reaction vessel. Compound **2** was readily isolable in 62% yield.

Hydrolysis of **6** (aqueous tetrahydrofuran, room temperature, 7 days) led to lactam **1** (52%) and, interestingly, the 2-morpholinyl derivative **3** as a by-product in 8% yield. When the hydrolysis was conducted in refluxing aqueous tetrahydrofuran, compound **3** was obtained in 21% yield. Higher yield of **3** was obtained when **6** was treated with morpholine (74%). Pyrolysis of **6** in refluxing 1,2,4-trichlorobenzene (214 °C) afforded **3** in 26% yield along with an isomeric product **4** obtained in 17% yield. The assignment of the 3-amino-2-morpholinylquinoline structure **4** was correlated with a synthesis from 3-amino-6-chloro-2-(di-4-morpholinyl)phosphinyloxy-4-phenylquinoline (**8**)[7] and morpholine. The fact that **4** is a secondary pyrolysis product derived from **3** was demonstrated by the conversion of **3** to **4** under similar conditions. The pyrolytic conversion of the di-4-morpholinylphosphinyloxy imine **6** to morpholinylimine **3** is an exemplification of the process proposed in the literature[11] to explain the conversion of secondary amides to their corresponding amidines by heating with amides of phosphoric acid. Although phosphorodiamidates of type **6** have been proposed as intermediates in these reactions, it appears that in no case have they been isolated.



The reaction of **8**, an aromatic dimorpholinylphosphinyloxy imine, with morpholine was quite sluggish compared with the same reaction involving **6**. Since the condition used was vigorous (refluxing morpholine, 46 h, 12% yield), it is not clear if this reaction proceeds via intermolecular or intramolecular displacement. Both types of reaction have been observed in the case of **6**. To show that nucleophilic displacement can occur in the case of **8**, the compound was treated with the anion of methyl mercaptan in refluxing methyl Cellosolve (2 h). The 2-methylthioquinoline derivative **12** was isolated in 26% yield.

A third dimorpholinylphosphinyloxy imine examined was 7-chloro-5-(di-4-morpholinyl)phosphinyloxy-2-methylamino-3*H*-1,4-benzodiazepine (**13**).[7] The reactivity of **13** toward nucleophiles was intermediate between that of compound **6** and of compound **8**. Heating was required (steam bath, 24 h) for the complete reaction of **13** with methylamine. The 5-methylamino derivative **14** was obtained in 48% yield. When a solution of **13** in tetrahydrofuran containing triethylamine was saturated with hydrogen sulfide and allowed to stand overnight at room temperature, double thiation occurred resulting in the isolation of the 2,5-dithione **15** in 75% yield.

As an alternate leaving group in these displacement reactions, we investigated the replacement of the morpholinyl groups in the di-4-morpholinylphosphinyloxy function with phenoxy groups. When the anion of lactam **1** was phosphorylated[7] with diphenyl phosphorochloridate, the desired imidoyl phosphate **17** could not be isolated. The presence of **17** in the reaction mixture is, however, suggested by the fact that quenching the mixture with methylamine resulted in the formation of the amidine **9a** (20% yield).

Experimental Section

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one[12] (1) from the Hydrolysis of 7-Chloro-2-(di-4-morpholinyl)-phosphinyloxy-5-phenyl-3*H*-1,4-benzodiazepine (6).[7] A solution of 245 mg (0.5 mmol) of **6** in 5 ml of tetrahydrofuran was stirred with 1.5 ml of water for 7 days. Tetrahydrofuran was evaporated. The residue was partitioned between water and methylene chloride. The organic layer was dried and evaporated. The products were separated by preparative TLC on four silica gel plates developed in 10% methanol–ethyl acetate. The front band (R_f 0.69) was collected, eluted with

10% methanol–ethyl acetate, and evaporated. Crystallization of the residue from ether gave 70 mg (52%) of colorless prisms, mp 215–217 °C. This material was identified as **1** by TLC, mixture melting point, and comparison of infrared spectra with an authentic sample.[12]

The major by-product (R_f 0.53) was collected, eluted with 10% methanol–ethyl acetate, and evaporated. Crystallization of the residue from hexane gave 14 mg (8%) of colorless solids, mp 75–85 °C dec. This material was identified as 7-chloro-2-(4-morpholinyl)-5-phenyl-3*H*-1,4-benzodiazepine (**3**) by TLC, mixture melting point, and comparison of infrared spectra with **3** prepared below.

When this experiment was repeated with heating of the aqueous tetrahydrofuran solution at reflux for 30 h instead of the 7 days at room temperature, we obtained **1** and **3** in 26 and 21%, respectively.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (2).[3c] **A. From 6.** To a solution of 74 mg (1.0 mmol) of acethydrazide in 5 ml of butanol was added 245 mg (0.5 mmol) of 7-chloro-2-(di-4-morpholinyl)phosphinyloxy-5-phenyl-3*H*-1,4-benzodiazepine (**6**). The mixture was heated to reflux for 1 h. The solvent was evaporated and the residue was partitioned between methylene chloride and water. The methylene chloride layer was washed with water, dried, and evaporated. The residue was crystallized from methylene chloride–ether to give, in two crops, 124 mg (80%) of **2**, mp 226–228 °C. This material was found identical (TLC, mixture melting point, ir) with a sample prepared by the literature[3c] procedure.

B. From 1 without Isolation of Intermediates. To a solution of 1.08 g (4.0 mmol) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**1**) in 20 ml of dry tetrahydrofuran at room temperature was added 230 mg of a 50% dispersion of sodium hydride in oil (4.8 mmol of hydride). The mixture was warmed gently on the steam bath for approximately 1 h until hydrogen evolution stopped. Di-4-morpholinylphosphinic chloride (**16**, 1.53 g, 6.0 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. To this mixture was then added a solution of 593 mg (8 mmol) of acethydrazide in 5 ml of butanol and stirring was continued at room temperature for 10 min. Solvents were evaporated and the residue was dissolved in 10 ml of butanol and heated to reflux for 1 h. Butanol was evaporated and the residue was partitioned between methylene chloride and water. The methylene chloride layer was dried and evaporated. The residue was crystallized from methylene chloride–ether to give 745 mg (62%) of **2**, mp 223–225 °C. This material was identical with the material prepared above by TLC and comparison of infrared spectra.

7-Chloro-2-(4-morpholinyl)-5-phenyl-3*H*-1,4-benzodiazepine (3). A. From 6 with Morpholine. To a stirred solution of 4.9 g (10 mmol) of **6** in 220 ml of tetrahydrofuran at room temperature was added 2.2 g (25 mmol) of morpholine. Stirring was continued at room temperature overnight. Tetrahydrofuran was evaporated. The residue was partitioned between water and methylene chloride. The organic layer was dried and evaporated. Crystallization of the residue from hexane over dry ice gave 2.5 g (74%) of the desired product. Recrystallization from hexane afforded colorless prisms: mp 80–90 °C (indefinite); ir (KBr) 1560 and 1585 cm^{-1}; uv max (2-PrOH) 233 nm (ϵ 27 250), 272 (18 650), 285 (sh, 17 400), and 351 (3100); mass spectrum *m/e* 339 (M^+).

Anal. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.16; H, 5.34; N, 12.37. Found: C, 67.04; H, 5.36; N, 12.10.

B. From 6 in Aqueous Tetrahydrofuran. Compound **3** occurred as a significant by-product in the hydrolysis of **6** described above.

C. From the Pyrolysis of 6. A suspension of 978 mg (2.0 mmol) of **6** in 10 ml of 1,2,4-trichlorobenzene (bp 214 °C) was heated to reflux for 0.5 h. The resulting solution was concentrated at 80–90 °C and applied directly on 24 preparative TLC plates, then developed in methanol–ethyl acetate (1:10 v/v). The main product **3** (R_f 0.59) was isolated and crystallized from petroleum ether to give 233 mg (26%) of colorless prisms, mp 80–90 °C (indefinite). A major by-product **4** (R_f 0.74) was also isolated and crystallized from petroleum ether to give 153 mg (17%) of light yellow prisms, mp 178–180 °C. This material was found to be identical (TLC, mixture melting point) with **4** as prepared below.

3-Amino-6-chloro-2-(4-morpholinyl)-4-phenylquinoline (4). A. From 8. A mixture of 245 mg (0.5 mmol) of 3-amino-6-chloro-2-(di-4-morpholinyl)phosphinyloxy-4-phenylquinoline (**8**)[7] and 5 ml of morpholine was heated to reflux for 46 h. Morpholine was evaporated. The gum was separated by preparative TLC on five silica gel plates developed in ether. The desired product (R_f 0.81) was isolated and crystallized from ethyl acetate to give 20 mg (12%) of light yellow prisms: mp 178–180 °C; ir (KBr) 3330 (broad), 1585, and 1410 cm^{-1}; uv max (2-PrOH) 232 nm (ϵ 32 800), 255 (37 000), and 353 (11 300); mass spectrum *m/e* 339 (M^+).

Anal. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.16; H, 5.34; N, 12.37. Found: C, 67.34; H, 5.28; N, 12.68.

B. From 3. A solution of 170 mg (0.5 mmol) of **3** in 2 ml of 1,2,4-trichlorobenzene containing 0.1 mmol of *p*-toluenesulfonic acid was heated to reflux for 4 h. The mixture was separated by preparative TLC on five silica gel plates developed in ether. The desired product **4** (R_f 0.81) was isolated and crystallized from ethyl acetate to give 60 mg (35%) of light yellow prisms, mp 178–180 °C. Mixture melting point with **4** from A above was undepressed.

7-Chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine (5a).[8,13] To a solution of 245 mg (0.5 mmol) of **6** in 5 ml of methanol at room temperature was added 82 mg (1.5 mmol) of sodium methoxide. The mixture was left at room temperature overnight. Methanol was evaporated and the residue was slurried with ether. Insoluble salts were removed by filtration. The clear ether solution was evaporated. Crystallization of the residue from petroleum ether yielded 124 mg (87%) of **5a**, mp 94–97 °C. This material was found to be identical (TLC, mixture melting point) with a reference[13] sample of **5a**.

7-Chloro-2-(2-hydroxyethoxy)-5-phenyl-3*H*-1,4-benzodiazepine (5b). A suspension of 1.95 g (4.0 mmol) of **6** in 10 ml of ethylene glycol containing 4 ml of triethylamine was heated on a steam bath for 2 h. A clear solution formed soon after heating began. Triethylamine was removed in vacuo. The ethylene glycol solution was poured into ice water precipitating solids which were collected and washed thoroughly with water. Remaining water was removed from the solid by dissolving the solid in ether, drying over sodium sulfate, and evaporation of ether. Crystallization of the residue from ether–hexane gave 1.03 g (82%) of colorless prisms: mp 142–144 °C; ir (KBr) 3250 and 1645 cm^{-1}; uv max (2-PrOH) 218 nm (ϵ 33 200), 255 (sh, 14 800), and 322 (2260); NMR ($CDCl_3$) δ 2.96 (t, 1, OH), 3.9 (m, 2, CH_2OH), 4.11 (broad s, 2 CH_2), 4.4 (m, 2, CH_2O), and 7.2–7.6 ppm (m, 8, aromatic).

Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.83; H, 5.08; N, 9.05.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (7).[3b] To a stirred solution of 245 mg (0.50 mmol) of **6** in 10 ml of tetrahydrofuran containing 0.5 ml of triethylamine at room temperature was introduced a stream of hydrogen sulfide gas until TLC indicated that all the starting material was consumed (15 min). Tetrahydrofuran was evaporated. The residue was partitioned between methylene chloride and water. The methylene chloride layer was dried and evaporated. Crystallization of the residue from methanol yielded in two crops 115 mg (78%) of **7**, mp 243–245 °C. This material was identified by TLC, mixture melting point, and ir comparisons with an authentic sample.

7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (9a).[14] **A. From Di-4-morpholinylphosphinyloxy Imine 6.** To a solution of 487 mg (1.0 mmol) of **6** in 10 ml of tetrahydrofuran at room temperature was introduced a stream of methylamine gas for 10 min. Solids precipitated during the addition. The solvent was evaporated and the residue was partitioned between methylene chloride and water. The methylene chloride layer was dried and evaporated. Crystallization of the residue from methylene chloride–hexane yielded, in two crops, 275 mg (96%) of **9a**, mp 245–247 °C. This material was identified by TLC, mixture melting point, and ir comparisons with an authentic sample.[14]

B. By Way of Diphenoxyphosphinyloxy Imine 17. To a solution of 2.7 g (10 mmol) of 1 in 100 ml of dry tetrahydrofuran at room temperature was added 576 mg of 50% dispersion of sodium hydride in mineral oil (12 mmol of hydride). The mixture was warmed gently on the steam bath for approximately 1 h until hydrogen evolution stopped. To this mixture was added 4 g (15 mmol) of diphenyl phosphorochloridate. The mixture was kept at room temperature overnight. Insoluble salts were removed by filtration and the solvent was evaporated. The residue was dissolved in 50 ml of tetrahydrofuran and methylamine gas was bubbled into the solution at room temperature for 0.5 h. Tetrahydrofuran was evaporated and the residue was partitioned between methylene chloride and water. The methylene chloride layer was dried and evaporated. Crystallization from methylene chloride–hexane yielded, in two crops, 540 mg (20%) of **9a**, mp 245–247 °C, identified by TLC, mixture melting point, and comparison of ir spectra.

7-Chloro-2-(2-methoxycarbonyl)hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (9b). To a stirred solution of 9.8 g (20 mmol) of **6** in 200 ml of tetrahydrofuran at room temperature was added 3.6 g (40 mmol) of methyl hydrazinocarboxylate. The resulting orange solution was stirred at room temperature for 2 h. Tetrahydrofuran was evaporated. The residue was partitioned between water and methylene chloride. The methylene chloride layer was dried and evaporated. Crystallization of the residue from ethyl acetate gave 5.8

g (84%) of the product, mp 198–200 °C dec. Recrystallization from ethyl acetate afforded colorless needles: mp 201–203 °C dec; ir (KBr) 3200, 1690, and 1610 cm^{-1}; uv max (2-PrOH) 210 nm (sh, ϵ 18 600), 230 (sh, 15 000), 258 (13 350), and 337 (900).

Anal. Calcd for $C_{17}H_{15}ClN_4O_2$: C, 59.57; H, 4.41; N, 16.35. Found: C, 59.30; H, 4.47; N, 16.32.

7-Chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2*H*-1,4-benzodiazepine (10).[9] To a mixture of 1.0 ml of nitromethane and 5 ml of dry dimethylformamide was added 53 mg of a 50% dispersion of sodium hydride in mineral oil (1.1 mmol hydride). After 1 h at room temperature, under nitrogen, 489 mg (1.0 mmol) of **6** was added. After stirring at room temperature for 2 h, dimethylformamide was evaporated (about 80 °C). The residue was partitioned between methylene chloride and an aqueous layer which is acidified with a slight excess of acetic acid. The methylene chloride layer was dried with anhydrous sodium sulfate and evaporated. Separation of the product mixture by preparative TLC (silica gel, developed in 10% methanol in ethyl acetate v/v) afforded pure **10** (R_f 0.72), which upon crystallization from methanol weighed 85 mg (27%), mp 178–180 °C. This material is identical with a reference sample[9] of **10** (TLC, mixture melting point, ir).

7-Chloro-1,3-dihydro-2-(dimethoxymalonylidene)-5-phenyl-2*H*-1,4-benzodiazepine (11).[5] To a solution of 489 mg (1.0 mmol) of **6** in 5 ml of dry dimethylformamide at room temperature was added 130 mg (1.15 mmol) of potassium *tert*-butyl alcoholate and 0.5 ml of dimethyl malonate. The resulting dark mixture was kept at room temperature for 2 h, then warmed on the steam bath for 0.5 h. The solvent was evaporated and the desired product (R_f 0.62, ether) was isolated by using preparative thin layer chromatography. Crystallization from 2-propanol yielded 50 mg (13%) of **11**, mp 130–133 °C. This material was identical with an authentic sample[5] of **11** by TLC and comparision of infrared spectra.

3-Amino-6-chloro-2-methylthio-4-phenylquinoline (12). To a stirred solution of 489 mg (1.0 mmol) of 3-amino-6-chloro-2-(di-4-morpholinyl)phosphinyloxy-4-phenylquinoline (**8**) in 30 ml of dry tetrahydrofuran was added 4 ml of a 1 M solution of sodium salt of methyl mercaptan in Cellosolve. The reaction mixture was heated to reflux for 2 h. The resulting suspension was then allowed to cool to room temperature at which time the insoluble salts were removed by filtration. The filtrate was concentrated to an oily gum. The gum was separated by preparative TLC (six silica gel plates developed in a 1:9 v/v mixture of ether and benzene). The desired product (R_f 0.80) was isolated and crystallized from ether–hexane. A total of 79 mg (26%) of light yellow prisms was collected: mp 115–117 °C; ir (KBr) 3470 and 3380 (NH_2) and 1610 and 1485 cm^{-1} (aromatic).

Anal. Calcd for $C_{16}H_{13}ClN_2S$: C, 63.89; H, 4.57; N, 9.31. Found: C, 64.02; H, 4.37; N, 9.63.

7-Chloro-2,5-bis(methylamino)-3*H*-1,4-benzodiazepine (14). A solution of 1.00 g (2.2 mmol) of 7-chloro-5-(di-4-morpholinyl) phosphinyloxy-2-methylamino-3*H*-1,4-benzodiazepine (**13**) in 30 ml of a 3.8 M solution of methylamine in tetrahydrofuran was heated in a stoppered glass pressure bottle on a steam bath for 24 h. The solution was concentrated to a gum. The gum was dissolved in a small volume of ethanol. Addition of ethanolic hydrogen chloride followed by ether afforded 500 mg of hydrochloride salt, mp 276–278 °C.

The salt was dissolved in water and basified with aqueous ammonia to liberate the free base. The base was isolated by extraction with methylene chloride. Crystallization from methylene chloride afforded 250 mg (48%) of colorless prisms, mp 235–237 °C. Recrystallization from ethanol raised the mp to 248–250 °C; ir (KBr) 3275 and 3200 cm^{-1} (NH) and broad unresolved bands between 1590 and 1490 cm^{-1}; uv max (CH_3OH) 218 nm (sh, ϵ 18 500), 272 (14 400), and 319 (2900); mass spectrum *m/e* 236 (M^+).

Anal. Calcd for $C_{11}H_{13}ClN_4$: C, 55.82; H, 5.54; N, 23.67. Found: C, 55.53; H, 5.44; N, 23.72.

7-Chloro-1,2,3,4-tetrahydro-5*H*-2,5-dithione (15). To a stirred suspension of 442 mg (1.0 mmol) of 7-chloro-5-(di-4-morpholinyl)-phosphinyloxy-2-methylamino-3*H*-1,4-benzodiazepine (**13**) and 1.0 ml of triethylamine in 50 ml of dry tetrahydrofuran at room temperature was introduced a stream of bubbles of hydrogen sulfide gas for 1 h. Solids gradually dissolved and solution turned yellow. The solution was allowed to stand at room temperature overnight. Tetrahydrofuran was evaporated. The residue was stirred with 50 ml of water and 50 ml of methylene chloride. Solids which precipitated were collected and washed with methylene chloride to give 180 mg (75%) of **15**, mp 273–274 °C dec. Recrystallizations from methanol afforded yellow needles: mp 273 ° dec; ir (KBr) 3150, 1550, 1465, 1380, 1185, and 1165 cm^{-1}; uv max (CH_3OH) 210 nm (ϵ 22 900) 230 (sh, 14 500), 303 (21 100), and 342 (sh, 11 100); mass spectrum *m/e* 242 (M^+); NMR (Me_2SO-d_6) δ 4.18 (broad s, 2, CH_2), 7.23 (d, J = 9 Hz, 1, H-9), 7.61 (dd, 1, H-8), 8.04 (d, J = 2.5 Hz, 1, H-6), 11.22 (broad, 1, NH), and 12.50 ppm (broad, 1, NH).

Anal. Calcd for $C_9H_7ClN_2S_2$: C, 44.53; H, 2.91; N, 11.54; Cl, 14.60; S, 26.42. Found: C, 44.65; H, 3.27; N, 11.52; Cl, 14.50; S, 26.16.

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Registry No.—**3,** 59318-08-0; **4,** 59318-09-1; **5b,** 59318-10-4; **6,** 59318-11-5; **8,** 59318-12-6; **9b,** 59318-13-7; **12,** 59163-16-5; **13,** 59318-14-8; **14,** 59318-15-9; **14** HCl, 59318-16-0; **15,** 59318-17-1; morpholine, 110-91-8; ethylene glycol, 107-21-1; methyl hydrazinocarboxylate, 6294-89-9.

References and Notes

(1) Part 75: A. Walser, G. Zenchoff, and R. I. Fryer, *J. Med. Chem.*, in press.
(2) (a) R. Roger and D. G. Neilson, *Chem. Rev.*, **61,** 179 (1961); (b) S. R. Sandler and W. Karo, "Organic Functional Group Preparations", Vol. III, Academic Press, New York, N.Y., 1972, 268; (c) S. Patai, Ed., "The Chemistry of Amidines and Imidates", Wiley, New York, N.Y., 1975; (d) R. Bonnett in "The Chemistry of the Carbon-Nitrogen Double Bond", S. Patai, Ed., Interscience, New York, N.Y., 1970, p 597.
(3) (a) W. Walter and J. Voss in "The Chemistry of Amides", J. Zabicky, Ed., Interscience, New York, N.Y., 1970, p 383; (b) G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, **29,** 231 (1964); (c) J. B. Hester, Jr., A. D. Rudzik and B. V. Kamdar, *J. Med. Chem.*, **14,** 1078 (1971).
(4) R. I. Fryer, J. V. Earley, G. F. Field, W. Zally, and L. H. Sternbach, *J. Org. Chem.*, **34,** 1143 (1959).
(5) A. Walser and R. I. Fryer, *J. Org. Chem.*, **40,** 153 (1975).
(6) (a) L. O. Randall, W. Schallek, L. H. Sternbach, and R. Y. Ning in "Psychopharmacological Agents", Vol. III, M. Gordon, Ed., Academic Press, New York, N.Y., 1974, and references cited therein; (b) S. Garattini, E. Mussini, and L. O. Randall, Ed., "Benzodiazepines", Raven Press, New York, N.Y., 1973.
(7) R. Y. Ning, R. I. Fryer, P. B. Madan, and B. C. Sluboski, *J. Org. Chem.*, preceding paper in this issue.
(8) A 2-cyano-1,4-benzodiazepine, an imidoyl cyanide, has been prepared recently and found to be reactive toward nucleophiles: D. L. Coffen, J. P. DeNoble, E. L. Evans, G. F. Field, R. I. Fryer, D. A. Katonak, B. J. Mandel, L. H. Sternbach, and W. J. Zally, *J. Org. Chem.*, **39,** 167 (1974).
(9) A. Walser and R. I. Fryer (Hoffmann-La Roche), Belgium Patent 833 248, (March 10, 1976).
(10) K. Meguro, H. Tawada, H. Miyano, Y. Sato, and Y. Kuwada, *Chem. Pharm. Bull.*, **21,** 2382 (1973).
(11) (a) E. A. Arutyunyan, V. I. Gunar, E. P. Gracheva, and S. I. Zavyalov, *Bull. Acad. Sci. USSR*, 587 (1969); *Izv. Akad. Nauk SSSR, Ser. Khim.*, 655 (1969); *Chem. Abstr.*, **71,** 30453h (1969); (b) A. Rosowsky and N. Papathanasopoulos, *J. Heterocycl. Chem.*, **9,** 1235 (1972); (c) E. B. Pedersen and S. O. Lawesson, *Tetrahedron*, **29,** 4205 (1973), and references cited therein.
(12) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stempel, *J. Org. Chem.*, **27,** 3788 (1962).
(13) J. V. Earley and R. I. Fryer, Belgian Patent 772 518 (1970).
(14) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26,** 1111 (1961).

Synthesis of 5*H*,12*H*-Quinazolino[3,2-*a*][3,1]benzoxazine-5,12-diones

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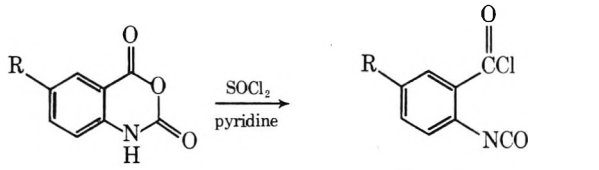
A coproduct of 5-chloro-2-isocyanatobenzoyl chloride (**2b**) produced in the reaction of 5-chloroisatoic anhydride (**1b**) with thionyl chloride and a catalytic amount of pyridine has been identified as 3,10-dichloro-5*H*,12*H*-quinazolino[3,2-*a*][3,1]benzoxazine-5,12-dione (**3**). As a result, a new synthesis of the tetracyclic ring system represented by **3**, from isatoic anhydrides and o-cyanatobenzoyl chlorides, was developed. The mechanism for the formation of quinazolinobenzoxazinediones by this novel method is discussed.

We recently reported[1] the use of 2-isocyanatobenzoyl chloride (**2a**) and its-5-chloro analogue (**2b**) in the preparation of 3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-diones. The reaction of isatoic anhydride (**1a**) with thionyl chloride in the presence of a catalytic amount of pyridine[2] yielded a solution which, after 24 h, was concentrated and distilled to afford 82% of **2a**. Treatment of 5-chloroisatoic anhydride (**1b**) with thionyl chloride in the presence of a catalytic amount of pyridine yielded a solution only after additional thionyl chloride and dioxane had been added, and reflux had been maintained for 3 weeks.[1] Concentration of this solution yielded a yellow liquid, which was distilled to afford 5-chloro-2-isocyanatobenzoyl chloride (**2b**) in 31% yield, and a yellow solid (Scheme I).

Scheme I



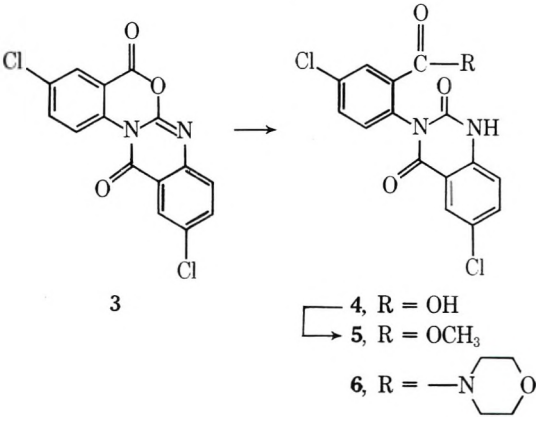
1a, R = H — **2a**, R = H (82%)
b, R = Cl — **b**, R = Cl (31%) + **3** (42%)

On the basis of spectral, chemical, and analytical data, we have now identified this yellow solid, which was produced in 42% yield, as 3,10-dichloro-5*H*,12*H*-quinazolino[3,2-*a*]-[3,1]benzoxazine-5,12-dione (**3**). The mass spectrum (70 eV) of **3** displayed a molecular ion at *m/e* 332 and combustion analysis indicated a molecular formula of $C_{14}H_6Cl_2N_2O_3$. The NMR spectrum of **3** indicated only the presence of aromatic protons, and the infrared spectrum showed only CH stretching above 3000 cm^{-1}, and intense absorption bands at 1765, 1695, and 1620 cm^{-1}, which we assign to the benzoxazinone carbonyl, quinazolinone carbonyl, and C=N groups of **3**, respectively.

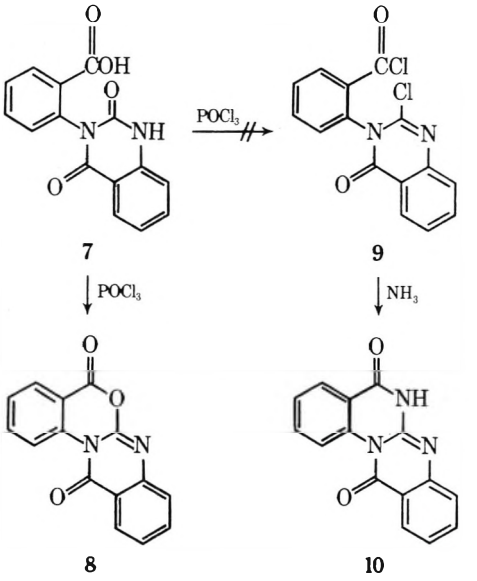
Quinazolobenzoxazinedione **3** was reactive, as would be predicted,[3] toward nucleophiles. Attempted recrystallization of **3** from dioxane produced 5-chloro-2-[6-chloro-1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoic acid (**4**), from the small amount of water present in the solvent. Treatment of **4** with 3-methyl-1-*p*-tolyltriazine (TMT) gave methyl ester **5**, which was also produced by dissolving **3** in methanol and dimethyl sulfoxide. Brief treatment of **3** with morpholine produced the morpholine amide **6**. See Scheme II.

The parent compound of the ring system represented by **3**, 5*H*,12*H*-quinazolino[3,2-*a*][3,1]benzoxazine-5,12-dione (**8**), has been reported by Doleschall and Lempert.[3] In an attempt to prepare 5*H*-quinazolino[3,2-*a*]quinazoline-5,12(6*H*)-dione (**10**), a compound isosteric with **7**, Doleschall and Lempert first treated 2-[1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoic acid (**7**) with phosphorus oxychloride.[4] These authors envisioned the production of acid chloride **9** from this reaction,

Scheme II



Scheme III

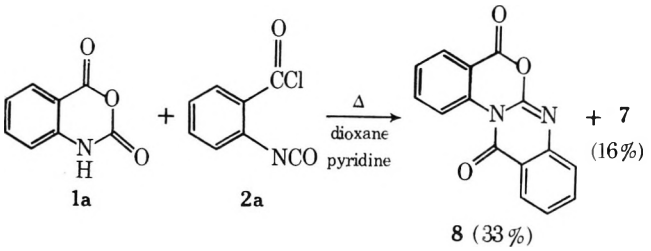


which they could then react with ammonia to give **10**,[5] and with primary amines to yield 6-substituted derivatives of **10**. Instead, cyclodehydration occurred to produce **8** rather than the expected **9** (Scheme III). The structure of **8** was confirmed and other possible isomeric products were eliminated on the basis of chemical reactivity and spectral data.

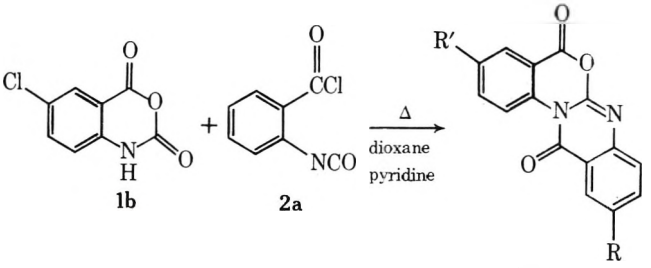
We have also prepared compound **8** by treating isatoic anhydride (**1a**) and 2-isocyanatobenzoyl chloride (**2a**) with a catalytic amount of pyridine in dioxane at reflux. Acid **7**, which was a coproduct in this reaction, was probably produced from **8** by hydrolysis during workup (Scheme IV).

Several mechanistic possibilities for the formation of **8** were considered at this point. The results shown in Scheme IV did not rule out mechanisms which could be envisioned for the

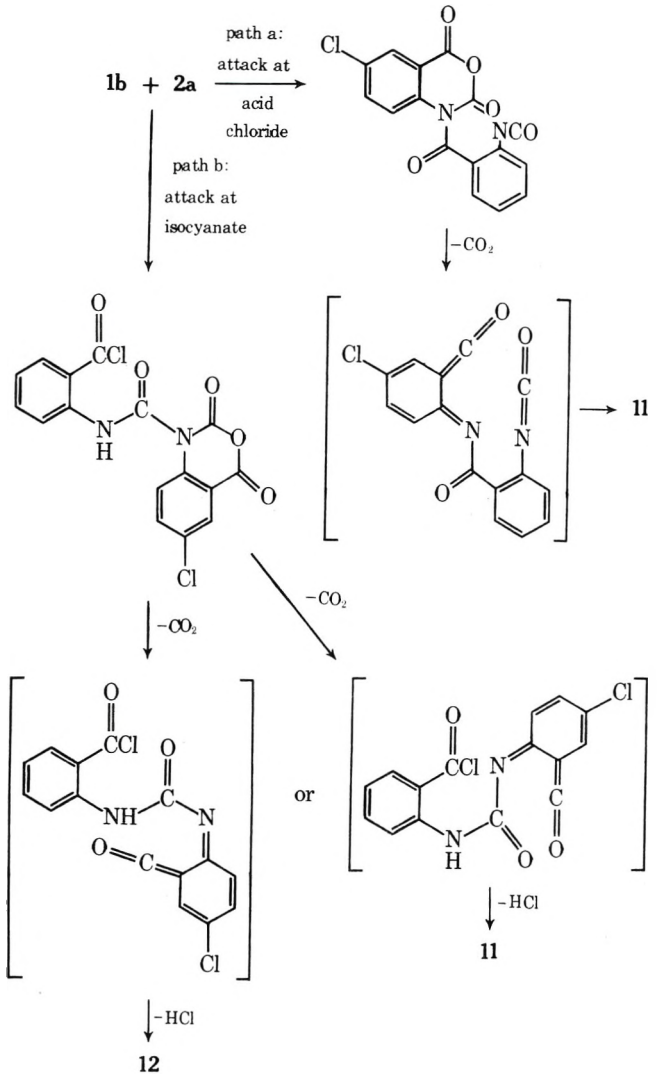
Scheme IV



Scheme V

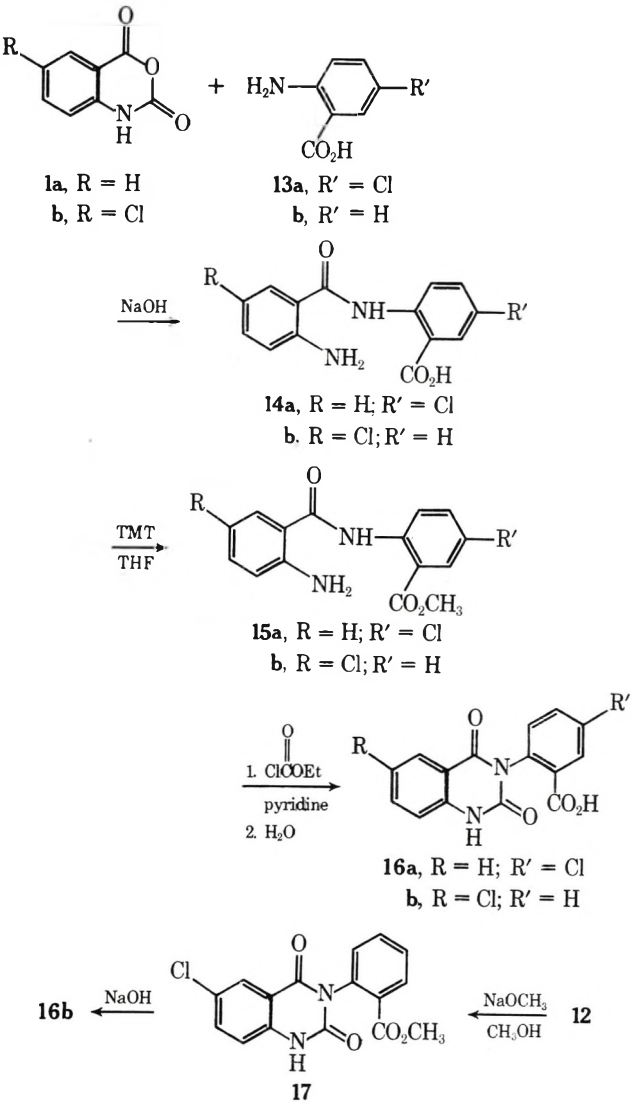


Scheme VI



production of 8 from either **1a** alone or **2a** alone. An experiment which did rule out these possibilities, however, is shown in Scheme V. When equimolar amounts of 5-chloroisatoic anhydride (**1b**) and 2-isocyanatobenzoyl chloride (**2a**) and a catalytic amountof pyridine were heated at reflux in dioxane until **2a** was no longer present, a 60% yield of a single chloroquinazolinobenzoxazinedione, either **11** or **12**, was obtained.

Scheme VII



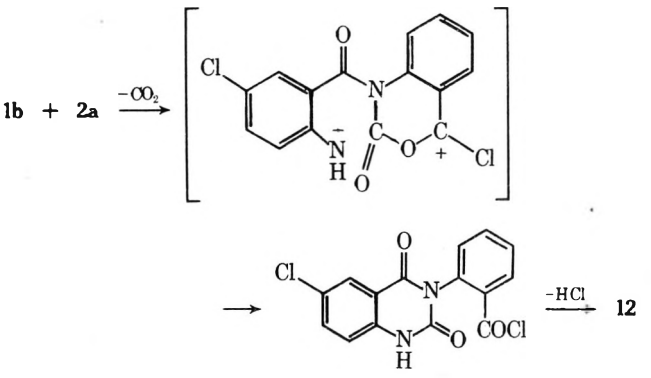
Scheme VI indicates possible mechanistic pathways for the production of a chloroquinazolobenzoxazinedione by nucleophilic attack of **1b** on **2a**. Since previous work[1] indicated that the carboxylic acid chloride group in *o*-isocyanatobenzoyl chlorides was more susceptible to nucleophilic attack than the isocyanato group, we initially favored the mechanism depicted in path a.[6] Therefore, we chose to first determine, by an unequivocal synthetic route, whether compound **11** was the chloroquinazolinobenzoxazinedione produced from **1b** and **2a** (Scheme VI).

Reaction of isatoic anhydride (**1a**) with 5-chloroanthranilic acid (**13a**) produced anthraniloylanthranilic acid (**14a**). Methylation of **14a** with 3-methyl-1-*p*-tolyltriazine (TMT) produced ester **15a**. Treatment of **15a** with ethyl chloroformate in pyridine yielded, after workup, quinazolinedione **16a**.[7] Compound **16a** was compared with the product obtained when the reaction product from Scheme V was treated with sodium methoxide and then sodium hydroxide. Since these compounds were different, it was inferred that the reaction product from Scheme V was **12**, and that the ester obtained from treating **12** with sodium methoxide was **17**. See Scheme VII.

To confirm these findings, an authentic sample of **16b**[7] was then prepared from 5-chloroisatoic anhydride (**1b**) and anthranilic acid (**13b**) as shown in Scheme VII. The product from these reactions was identical in all respects with the product obtained when the reaction product from Scheme V was treated with sodium methoxide and then sodium hydroxide. If the reaction of **1b** and **2a** is initiated by nucleophilic attack of the nitrogen atom of **1b**, then path b[9] (Scheme VI) must be operative.

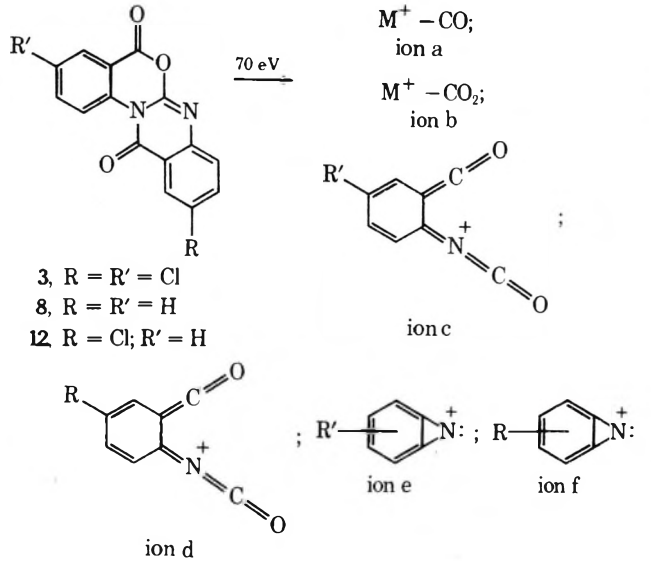
Another mechanism to be considered for the reaction of **1b** and **2a** is derived from one advanced by Staiger, Moyer, and Pitcher for the reaction of isatoic anhydride with phenyl isocyanate.[10] These authors state that "the nucleophilic nitrogen of the phenyl isocyanate attacks the number four carbon atom of isatoic anhydride, which is followed by loss of CO_2 and ring closure to the 3-phenyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline".[11] This mechanism, as applied to **1b** and **2a**, is shown in Scheme VIII. The only product predicted by this pathway is **12**, which is the observed product.

Scheme VIII



Mass spectral analysis of the product obtained from the reaction of **1b** and **2a** was not helpful in elucidating its structure. The major fragment ions observed for compounds **3**, **8**, and **12** are shown in Scheme IX. Although ions c and d are a

Scheme IX



degenerate pair for both compounds **3** and **8**, it is clear that they can arise from two different fragmentation pathways, since compound **12** produced the dissimilar ions c and d. The same is true for ions e and f. Thus, ions c, d, e, and f, all of different mass, are observed in the mass spectrum of **12**. It was, therefore, not possible to differentiate between structures **11** and **12** on the basis of mass spectral analysis.

Experimental Section[12]

3,10-Dichloro-5*H*,12*H*-quinazolino[3,2-*a*][3,1]benzoxazine-5,12-dione (3). The reaction of 5-chloroisatoic anhydride with $SOCl_2$ to produce **2b** in 31% yield and **3** in 42% yield (mp 213–218 °C) is described elsewhere.[1] Compound **3**: mp 238–242 °C (acetone); ir (Nujol) 1765 (benzoxazinone C=O), 1695 (quinazolinone C=O), 1620 cm^{-1} (C=N); NMR[13] (acetone-d_6) δ 8.44–7.17 (m, all protons); mass spectrum (70 eV) *m/e* (rel intensity) 334 (59), 332 (89), 306 (11), 304 (15), 290 (13), 288 (22), 182 (35), 180 (100), 126 (30), 124 (91).

Anal. Calcd for $C_{15}H_6Cl_2N_2O_3$: C, 54.08; H, 1.82; N, 8.41. Found: C, 54.30; H, 1.80; N, 8.66.

5-Chloro-2-[6-chloro-1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoic Acid (4). Compound **3** was quantitatively converted to **4** by crystallization from a large volume of wet dioxane. Alternatively, **3** was dissolved in wet Me_2SO to yield **4**, which was recovered by precipitation with water. Compound **4**: mp 303–305 °C: ir (Nujol) 3400–2400 (NH and OH), 1720 (acid C=O), 1670 (C=O); NMR (Me_2SO-d_6) δ 11.83 (s, 1, OH, D_2O exchangeable), 8.04–7.07 (m, 6, aromatic); mass spectrum (70 eV) *m/e* 350 (molecular ion).

Anal. Calcd for $C_{15}H_8Cl_2N_2O_4$: C, 51.31; H, 2.30; N, 7.98. Found: C, 51.63; H, 2.54; N, 7.74.

Methyl 5-Chloro-2-[6-chloro-1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoate (5). A. From 3. A 7.50-g (22.5 mmol) quantity of **3** was slurried with 75 ml of methanol and heated at reflux for 15 min. Solution had not resulted, and the ir of a concentrated aliquot of the mixture showed only starting material. A 40-ml volume of Me_2SO was added and reflux was maintained for 15 min. A small amount of insoluble material was removed by filtration. After 1 day, only a small amount of crystals had formed in the filtrate. The filtrate was warmed and the solution was diluted with water until cloudy, and then clarified by the addition of CH_3OH. White crystals then formed, which were collected in four crops to yield 5.32 g (65%) of **5** (mp 264–272 °C): mp 275–277 °C (CH_3OH); ir (Nujol) 3200 (NH), 1730 (ester (C=O), 1670 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 8.20–7.08 (m, 6, aromatic), 3.72 (s, 3, CO_2CH_3); mass spectrum (70 eV) *m/e* 364 (molecular ion).

Anal. Calcd for $C_{16}H_{10}Cl_2N_2O_4$: C, 52.63; H, 2.76; N, 7.67. Found: C, 52.54; H, 2.70; N, 7.57.

B. From 4. A 1.66-g (4.98 mmol) quantity of **4** and 0.746 g (5.00 mmol) of 3-methyl-1-*p*-tolyltriazine (TMT, Eastman) in 50 ml of tetrahydrofuran (THF) were heated at reflux for 14 h. The solution was filtered to remove a small amount of insoluble material and the filtrate was concentrated to dryness. The resulting solid was slurried with ether and the white solid was collected to yield 1.13 g (62%) of **5**, mp 271–275 °C , whose ir (Nujol) was identical with that prepared in part A.

4-[[5-Chloro-2-(6-chloro-1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl)phenyl]carbonyl]morpholine (6). A 7.50-g (22.5 mmol) quantity of **3** was mixed with 75 ml of morpholine and heated at reflux for 15 min. The brown solution was cooled and diluted with water to produce a precipitate which was collected and air dried to yield 8.48 g (90%) of crude **6**: mp 244–246 °C (EtOH–H_2O); ir (Nujol) 1725, 1670 cm^{-1}; NMR (Me_2SO-d_6) δ 8.13–7.17 (m, 6, aromatic), 3.58 (broad signal, 8, morpholino); mass spectrum (70 eV) *m/e* 419 (molecular ion)

Anal. Calcd for $C_{19}H_{15}Cl_2N_3O_4$: C, 54.30; H, 3.60; N, 10.00. Found: C, 54.39; H, 3.56; N, 9.94.

Reaction of Isatoic Anhydride (1a) with 1-Isocyanatobenzoyl Chloride (2a). To a solution of 16.3 g (0.100 mol) of **1a** in 300 ml of dry dioxane was added a solution of 18.2 g (0.100 mol) of **2a** in 60 ml of dioxane and 1 ml of pyridine. After 6 days, an ir of a concentrated aliquot indicated the absence of the isocyanate stretching band of **2a** at 2280 cm^{-1}. The solution was concentrated and the gummy material was lixiviated with ether. The gum was then triturated with acetone and the resulting white solid was collected and air dried to yield 8.80 g (33%) of 5*H*,12*H*-quinazolino[3,2-*a*][3,1]benzoxazine-5,12-dione (**8**), mp 224–226 °C: mp 228–229 °C (acetone) (lit.[3] mp 228 °C); ir (Nujol) 1775, 1710, 1695 cm^{-1}; mass spectrum (70 eV) *m/e* 264 (molecular ion).

Anal. Calcd for $C_{15}H_8N_2O_3$: C, 68.18; H, 3.05; N, 10.60. Found: C, 68.50; H, 3.14; N, 10.45.

The filtrate was concentrated to an oily material which crystallized and was collected and washed with acetone to yield 4.60 g (13%) of 2-[1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoic acid (**7**), mp 280–284 °C: mp 295–296 °C (C_2H_5OH) (lit.[14] mp 298–300 °C); ir (Nujol) 1710, 1660 cm^{-1} (broad).

Anal. Calcd for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.93. Found: C, 63.80; H, 3.56; N, 9.84.

Preparation of 10-Chloro-5*H*,12*H*-quinazolino[3,2-a][3,1]-benzoxazine-5,12-dione (12). A 19.8-g (0.100 mol) quantity of **1b** and 18.2 g (0.100 mol) of **2a** were mixed with 400 ml of dioxane and 1 ml of pyridine and heated at reflux. After 3 days solution had resulted and after 10 days, the ir of an aliquot indicated the absence of **2a**. The solution was evaporated to a small volume and the white solid was collected to give 17.9 g (60%) of **12**, mp 243–247 °C: ir (Nujol) 1700, 1770 cm^{-1}; mass spectrum (70 eV) *m/e* 298 (molecular ion).

Anal. Calcd for $C_{15}H_7ClN_2O_3$: C, 60.32; H, 2.36; N, 9.37. Found: C, 60.20; H, 2.44; N, 9.40.

Preparation of 5-Chloro-2-[1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoic Acid (16a). Following a literature procedure for the preparation of anthraniloylanthranilic acid,[15] isatoic anhydride (**1a**) and 5-chloroanthranilic acid (**13a**) were condensed to give 2-[(aminobenzoyl)amino]-5-chlorobenzoic acid (**14a**): mp 227–229 °C (ethyl acetate); ir 3350–2300 (broad stretching, with spikes at 3330 and 3230), 1650 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 12.12 (broad s, 1, NH), 8.67 (d, J = 9 Hz, 1, H ortho to CONH), 8.03 (d, J = 3 Hz, 1, H ortho to CO_2H), 7.86–6.57 (m, 5, remaining aromatic).

Anal. Calcd for $C_{14}H_{11}ClN_2O_3$: C, 57.84; H, 3.81; N, 9.63. Found: C, 58.10; H, 3.90, N, 9.46.

A 28.8-g (0.0991) mol) quantity of **14a** and 15.5 g (0.104 mol) of TMT in 200 ml of THF were stirred at 25 °C for 24 h. The solution was concentrated, slurried with ether–hexane, and the product collected to yield 22.1 g (73%) of methyl 2-[(aminobenzoyl)amino]-5-chlorobenzoate (**15a**): mp 157–158 °C (C_2H_5OH); ir (Nujol) 3460, 3340, and 3230 (NH and NH_2), 1685 (ester C=O), 1645 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ 11.77 (broad s, 1, NH), 8.85 (d, J = 9 Hz, 1, H ortho to CONH), 7.90 (d, J = 3 Hz, 1, H ortho to CO_2CH_3), 7.70–7.00 (m, 3, aromatic), 6.83–6.48 (m, 2, aromatic), 5.68 (broad s, 2, NH_2, D_2O exchangeable), 3.90 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{13}ClN_2O_3$: C, 59.11; H, 4.29; N, 9.19. Found: C, 59.40; H, 4.37; N, 9.43.

To 10.0 g (32.8 mmol) of **15a** in 100 ml of pyridine was added 3.56 g (32.8 mmol) of ethyl chloroformate and the solution was heated at reflux for 15 h. The solution was concentrated and partitioned between water and CH_2Cl_2 and the insoluble material was collected and air dried to yield 5.30 g (51%) of **16a**: mp 303–304.5 °C dec; ir (Nujol) 3250–2100 (NH and OH), 1715 (acid C=O), 1680 (amide C=O), 1650 cm^{-1} (urea C=O); NMR (Me_2SO-d_6) δ 11.63 (s, 1, CO_2H, D_2O exchangeable), 8.30–7.08 (m, 8, aromatic and NH).

Anal. Calcd for $C_{15}H_9ClN_2O_4$: C, 56.88; H, 2.86; N, 8.84. Found: C, 56.70; H, 3.06; N, 9.01.

Preparation of 2-[1,4-Dihydro-2,4-dioxo-6-chloro-3(2*H*)-quinazolinyl]benzoic Acid (16b). From 5-Chloroisatoic Anhydride (1b) and Anthranilic Acid (13b). Following a literature procedure for the preparation of anthraniloylanthranilic acid,[15] **1b** and **13b** were condensed to give 2-[(amino-5-chlorobenzoyl)amino]benzoic acid (**14b**) in 76% yield: mp 248–249 °C (C_2H_5OH); ir (Nujol) 3600–2300 (broad stretching, with spikes at 3420 and 3320), 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{11}ClN_2O_3$: C, 57.84; H, 3.81; N, 9.63. Found: C, 57.60; H, 3.87; N, 9.70.

Using the procedure described for the preparation of **15a**, **14b** was converted to methyl 2-[(2-amino-5-chlorobenzoyl)amino]benzoate (**15b**) in 88% yield: mp 158–159 °C (C_2H_5OH); ir (Nujol) 3460, 3350, and 3300 (NH and NH_2), 1680 (ester C=O), 1660 cm^{-1} (amide C=O); NMR (Me_2SO-d_6) δ 11.20 (s, 1, NH), 8.38 (d, J = 8 Hz, 1, H ortho to CO_2CH_3), 8.10–6.67 (m, 6, remaining aromatic), 6.64 (broad s, 2, NH_2), 3.90 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{13}ClN_2O_3$: C, 59.11; H, 4.29; N, 9.19. Found: C, 59.00; H, 4.28; N, 9.37.

Using the procedure described for the preparation of **16a**, **15b** was converted to **16b** (35%): mp 303 °C; ir (Nujol) 3250–2100 (NH and OH), 1720 (acid C=O), 1675 (amide C=O), 1650 cm^{-1} (urea C=O); NMR (Me_2SO-d_6) δ 11.80 (s, 1, CO_2H, D_2O exchangeable), 8.27–7.14 (m, 8, aromatic and NH).

Anal. Calcd for $C_{15}H_9ClN_2O_4$: C, 56.89; H, 2.86; N, 8.85. Found: C, 56.60; H, 2.94; N, 8.76.

B. From 12. A 3.60-g (12.0 mmol) quantity of **12** was slurried with 60 ml of CH_3OH and warmed on a steam bath. A solution of 25% $NaOCH_3$ in CH_3OH was added dropwise until solution resulted. Cooling produced white prisms which were collected to afford 82% of methyl 2-(6-chloro-1,4-dihydro-2,4-dioxo-3-quinazolinyl)benzoate (**17**): mp 269–272 °C; ir (Nujol) 3130 (NH), 1715 (ester C=O), 1650 cm^{-1} (C=O), NMR (Me_2SO-d_6) δ 8.14–7.70 (m, 2, aromatic protons ortho to C=O groups), 7.70–7.04 (m, 5, remaining aromatic), 3.69 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{11}ClN_2O_4$: C, 58.11; H, 3.35; N, 8.47. Found: C, 57.90; H, 3.44; N, 8.55.

A 2.00-g (6.05 mmol) quantity of **17** was slurried with 25 ml of 4 N NaOH and warmed gently until solution resulted. The solution was acidified with concentrated HCl and the resulting white solid was collected and air dried to yield 1.90 g (99%) of **16b**, mp 301–303 °C dec, which was spectrally identical with the material made in part A. A mixture melting point of this material and that made in part A was undepressed. A mixture melting point of **16b** and **16a** was substantially depressed (275–278 °C dec).

Acknowledgment. The authors wish to thank Barbara Isenbarger (Toxicology Department) for obtaining the spectral data.

Registry No.—**1a**, 118-48-9; **1b**, 4743-17-3; **2a**, 5100-23-2; **3**, 59187-49-4; **4**, 59187-50-7; **5**, 59187-51-8; **6**, 59187-52-9; **7**, 1701-95-7; **8**, 13969-02-3; **12**, 59187-53-0; **13a**, 635-21-2; **13b**, 118-92-3; **14a**, 40082-89-1; **14b**, 59187-54-1; **15a**, 59187-55-2; **15b**, 59187-56-3; **16a**, 59187-57-4; **16b**, 59187-58-5; **17**, 59187-59-6; morpholine, 110-91-8.

References and Notes

(1) N. P. Peet and S. Sunder, *J. Org. Chem.*, **40**, 1909 (1975).
(2) Y. Iwakura, K. Uno, and S. Kang, *J. Org. Chem.*, **31**, 142 (1966).
(3) G. Doleschall and K. Lempert, *Acta Chim. Acad. Sci. Hung.*, **48**, 77 (1966).
(4) Thionyl chloride in pyridine or phosphorus oxychloride in pyridine also effect the transformation of **7** to **8**.[3]
(5) (a) Compound **10** was first synthesized by K. Butler and M. W. Partridge, *J. Chem. Soc.*, 1512 (1959), and has more recently been prepared by others;[5b,c,d] (b) S. K. P. Sinha, *J. Indian Chem. Soc.*, **48**, 989 (1971); (c) M. Takahashi, S. Onizawa, and R. Shioda, *Nippon Kagaku Kaishi*, **8**, 1259 (1972); *Chem. Abstr.*, **78**, 72078q (1973); (d) S. Palazzo, L. I. Giannola, and M. Neri, *J. Heterocycl. Chem.*, **12**, 1077 (1975).
(6) A reviewer has suggested that the cycloaddition reaction which produces **11** in path a of Scheme VI is unlikely from a stereochemical standpoint.
(7) The direct conversion of **15a** and **15b** to **16a** and **16b**, respectively, was unexpected. We have previously reported[8] that compound **15**, where R = R′ = H, when treated with ethyl chloroformate in pyridine yields methyl 2-[[2-(ethoxycarbonylamino)benzoyl]amino]benzoate. The presence of the chlorine substituents in **15a** and **15b** has a profound effect on the reactions which produce **16a** and **16b**, respectively.
(8) N. P. Peet and S. Sunder, *J. Org. Chem.*, **39**, 1931 (1974).
(9) In path b of Scheme VI, the loss of HCl prior to the loss of CO_2 is as easily envisioned.
(10) R. P. Staiger, C. L. Moyer, and G. R. Pitcher, *J. Chem. Eng. Data*, **8**, 454 (1963). We thank a reviewer for calling this article to our attention.
(11) This quinazolinedione could also arise by nucleophilic attack of isatoic anhydride on phenyl isocyanate.
(12) Melting points are uncorrected. Ir spectra were recorded with a Perkin-Elmer 727B instrument; NMR spectra with Varian T-60 and Perkin-Elmer R32 (90 MHz) spectrometers; mass spectra with a Hitachi RMU-6D mass spectrometer. Combustion analyses were performed by Dow Analytical Laboratories.
(13) The NMR spectrum of **3** in Me_2SO-d_6 was identical with that of **4** taken in Me_2SO-d_6, indicating a rapid **3** → **4** conversion effected by water in the Me_2SO-d_6.
(14) G. Doleschall and K. Lempert, *Monatsh. Chem.*, **95**, 1083 (1964).
(15) R. P. Staiger and E. B. Miller, *J. Org. Chem.*, **24**, 1214 (1959).

Synthesis of 3,4-Dihydro-5*H*-1,3,4-benzotriazepin-5-ones

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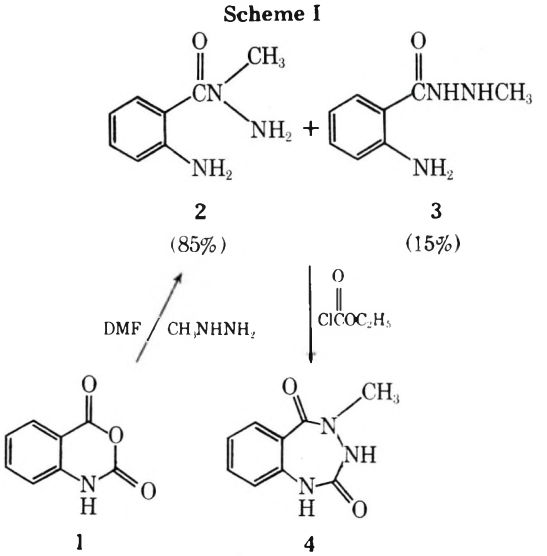
The reaction of isatoic anhydride (**1**) with methylhydrazine in dimethylformamide at 45–50 °C yielded predominantly 1-(o-aminobenzoyl)-1-methylhydrazine (**2**), whose structure was confirmed by conversion to the known 3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (**4**) with ethyl chloroformate. Hydrazide **2** was treated with triethyl ortho esters to produce 2-substituted 3,4-dihydro-4-methyl-5*H*-1,3,4-benzotriazepin-5-ones **5a–d**.

The reactions of isatoic anhydride with hydrazines to yield anthraniloyl hydrazides has been frequently used to generate starting materials for heterocyclic syntheses. Thus, isatoic anhydride has been reacted with hydrazine hydrate,[1] phenylhydrazine,[2] acylhydrazines,[3] carboalkoxyhydrazines,[4] symmetrical[5] and unsymmetrical[6,7] dialkylhydrazines, semicarbazides,[8] and 2-pyridylamidrazone[9] to yield the corresponding anthraniloyl hydrazides. We wish to report the reaction of methylhydrazine with isatoic anhydride (**1**) to yield 1-(o-aminobenzoyl)-1-methylhydrazine (**2**), and the utility of **2** in the preparation of 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones.

Treatment of a dimethylformamide (DMF) solution of isatoic anhydride[10] with methylhydrazine at 45–50 °C yielded, after concentration and distillation, a 76% yield of **2** and the isomeric 2-(o-aminobenzoyl)-1-methylhydrazine (**3**) in a ratio of 85:15 (by NMR), respectively.[11] That the mixture was predominantly **2** was confirmed by its reaction product with ethyl chloroformate. Treatment of the 85:15 mixture of **2** and **3** with ethyl chloroformate and triethylamine in methylene chloride gave a 26% yield of 3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (**4**), which was identical with an authentic sample of **4** whose unequivocal synthesis has been reported.[1] See Scheme I.

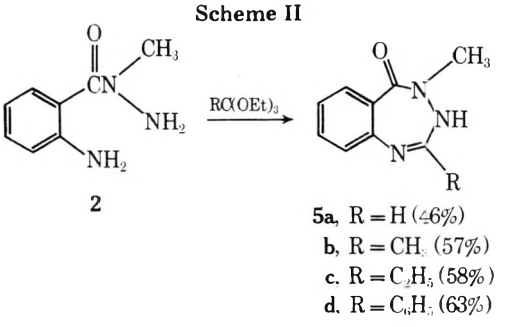
Scheme I



Hydrazide **2** (containing 15% of **3**)[12] was then reacted with triethyl orthoformate in ethanol to yield 3,4-dihydro-4-methyl-5*H*-1,3,4-benzotriazepin-5-one (**5a**). The other three benzotriazepinones shown in Scheme II were also prepared in good yield in similar fashion from the appropriate ortho esters.

The ultraviolet spectra of compounds **5a–d** all display absorption maxima at 229–231 nm with ϵ_{max} values of 17 000–21 000. These values are consistent with the expected[13] and reported[9a] values for the *N*-phenylimino chromophore.

Scheme II



The benzotriazepinones **5a–d** were prepared for pharmacological evaluation as central nervous system agents, as an integral part of our research efforts in this area. A recent report by Takahashi et al.[9a] describes the synthesis of similar compounds, namely, 3,4-dihydro-2-(2-pyridyl)-5*H*-1,3,4-benzotriazepin-5-ones.

Experimental Section[14]

Reaction of Isatoic Anhydride (1) with Methylhydrazine.[11] An 81.6-g (0.500 mol) quantity of **1**[10] was dissolved in 250 ml of dry DMF and warmed to 45 °C. A solution of 23.5 g (0.510 mol) of methylhydrazine (Aldrich) in 100 ml of DMF was added over a 15-min period. After 45 min at 45–50 °C, CO_2 evolution had ceased and the solution was concentrated to a viscous oil. Distillation afforded 62.7 g (76%) of an 85:15 mixture of **2** and **3**, respectively: bp 170–180 °C (1.0–3.0 mm); ir (neat) 3450, 3350, and 3250 (NH), 1610 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.45–6.94 (m, 2, aromatic), 6.90–6.35 (m, 2, aromatic), 4.70 (broad s, 4, both NH_2 groups), 3.10 and 2.60 (two singlets, 85:15 ratio, corresponding to NCH_3 groups in **2** and **3**, respectively);[15] mass spectrum (70 eV) *m/e* 165 (molecular ion).

Anal. Calcd for $C_8H_{11}N_3O$: C, 58.20; H, 6.71; N, 25.39. Found: C, 58.20; H, 6.57; N, 25.44.

Preparation of 3,4-Dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione (4). An 8.42-g (51.0 mmol) quantity of **2**, 5.53 g (51.0 mmol) of ethyl chloroformate, and 6.1 g (60 mmol) of triethylamine in 25 ml of CH_2Cl_2 were heated at reflux for 2 h. The resulting mixture (a white precipitate was present) was partitioned between water and CH_2Cl_2 and the organic layer was separated, dried (Na_2SO_4), and concentrated to yield 2.50 g (26%) of **4**, mp 266–267 °C (lit.[1] mp 266–267 °C). The infrared spectrum of **4** was identical with that of an authentic sample,[1] and a mixture melting point of **4** with an authentic sample was undepressed.

Preparation of 3,4-Dihydro-4-methyl-5*H*-1,3,4-benzotriazepin-5-one (5a). An 8.26-g (50.0 mmol) quantity of **2**[12] and 7.41 g (50.0 mmol) of triethyl orthoformate (Aldrich) in 20 ml of EtOH were heated at reflux for 15 h. The yellow solution was concentrated and the resulting yellow oil was triturated with EtOH to afford 4.0 g (46%) of **5a**: mp 159–161 °C (yellow prisms from EtOH); ir (Nujol) 3300 (NH), 1675 cm^{-1} (C=O); uv λ_{max} (96% EtOH) 231 nm (log ε 5.32), 260 sh (4.33), 288 sh (4.47); NMR ($CDCl_3$) δ 7.93–7.74 (m, 1, H ortho to C=O), 7.37–7.05 (m, 1, H para to C=O), 7.05–6.74 (m, 3, H para to N and CH=NH), 6.67–6.47 (m, 1, H ortho to N), 3.33 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 175 (molecular ion).

Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.60; H, 5.11; N, 23.88.

Preparation of 3,4-Dihydro-2,4-dimethyl-5*H*-1,3,4-benzotriazepin-5-one (5b). An 8.26-g (50.0 mmol) quantity of **2**[12] and 8.11 g (50.0 mmol) of triethyl orthoacetate (Aldrich) in 50 ml of EtOH were

heated at reflux for 12 h. The yellow solution was concentrated to a small volume. Trituration with ether afforded 5.35 g (57%) of **5b:** mp 132–133 °C (yellow prisms from EtOH–hexane); ir (Nujol) 3300 (NH), 1685 cm^{-1} (C=O); uv λ_{max} (95% EtOH) 228 nm (log ϵ 5.25), 252 sh (4.97), 288 sh (4.51); NMR ($CDCl_3$) δ 8.00–7.82 (m, 1, H ortho to C=O), 7.35–7.15 (m, 1, H para to C=O), 7.10–6.85 (m, 1, H para to N), 6.75–6.60 (m, 1, H ortho to N), 6.45 (broad s, 1, NH, D_2O exchangeable), 3.30 (s, 3, NCH_3), 2.07 (s, 3, CCH_3); mass spectrum (70 eV) *m/e* 189 (molecular ion).

Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.60; H, 5.92; N, 21.93.

Preparation of 2-Ethyl-3,4-dihydro-4-methyl-5*H*-1,3,4-benzotriazepin-5-one (5c). An 8.26-g (50.0 mmol) quantity of **2**[12] and 8.81 g (50.0 mmol) of triethyl orthopropionate (Aldrich) in 50 ml of EtOH were heated at reflux for 12 h. The light yellow solution was concentrated to a thick oil and crystallized from EtOH–hexane to afford 5.92 g (58%) of **5c** (yellow prisms): mp 103–104.5 °C; ir (Nujol) 3250 (NH), 1665 cm^{-1} (C=O); uv λ_{max} (95% EtOH) 229 nm (log ϵ 5.24), 251 sh (4.98), 285 sh (4.41); NMR ($CDCl_3$) δ 8.00–7.83 (m, 1, H ortho to C=O), 7.40–7.16 (m, 1, H para to C=O), 7.16–6.77 (m, 3, remaining aromatic plus NH), 3.37 (s, 3, NCH_3), 2.38 (q, J = 5 Hz, 2, CH_2), 1.17 (t, J = 5 Hz, 3, CH_2CH_3); mass spectrum (70 eV) *m/e* 203 (molecular ion).

Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.30; H, 6.49; N, 20.56.

Preparation of 3,4-Dihydro-4-methyl-2-phenyl-5*H*-1,3,4-benzotriazepin-5-one (5d). An 8.26-g (50.0 mmol) quantity of **2**[12] and 11.2 g (50.0 mmol) of triethyl orthobenzoate (ICN Pharmaceuticals, Inc.) in 40 ml of EtOH were heated at reflux for 12 h. The dark yellow solution was concentrated and the resulting solid was recrystallized from EtOH–ether to afford 7.90 g (63%) of **5d** (yellow prisms): mp 162–163.5 °C; ir (Nujol) 3260 (NH), 1610 cm^{-1} (C=O); uv λ_{max} (95% EtOH) 229 nm (log ϵ 5.34), 250 sh (4.25), 297 sh (4.81); NMR ($CDCl_3$) δ 8.03–7.85 (m, 1, H ortho to C=O), 7.85–7.65 (m, 2, aromatic), 7.55–7.26 (m, 4, aromatic), 7.15–6.82 (m, 2, aromatic), 6.79 (s, 1, NH, D_2O exchangeable), 3.43 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 251 (molecular ion).

Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.60; H, 5.23; N, 16.65.

Registry No.—**1,** 118-48-9; **2,** 59169-69-6; **3.** 59169-47-0; **5a,** 59169-76-5; **5b,** 59169-80-1; **5c,** 59187-60-9; **5d,** 59169-87-8; methylhydrazine, 60-34-4; triethyl orthoformate, 122-51-0; triethyl orthoacetate, 78-39-7; triethyl orthopropionate, 115-80-8; triethyl orthobenzoate, 1663-61-2.

References and Notes

(1) N. P. Peet and S. Sunder, *J. Org. Chem.*, **40**, 1909 (1975).
(2) (a) R. H. Clark and E. C. Wagner, *J. Org. Chem.*, **9**, 61 (1944). (b) The product of the reaction of isatoic anhydride with phenylhydrazine is 2-(*o*-aminobenzoyl)-1-phenylhydrazine.
(3) (a) S. K. Modi, V. Kumar, and K. S. Narang, *Indian J. Chem.*, **8**, 710 (1970); (b) A. L. Langis, U.S. Patent 3 542 767 (1970); *Chem. Abstr.*, **74**, 88089x (1971); (c) N. P. Peet, S. Sunder, and R. J. Cregge, *J. Org. Chem.*, following paper in this issue.
(4) S. Petersen, E. Tietze, F. Hoffmeister, and W. Wirth, British Patent 932 680 (1963); *Chem. Abstr.*, **60**, 4162*h* (1964).
(5) O. Hromatka, F. Krenmüller, and M. Knollmüller, *Monatsh. Chem.*, **100**, 934 (1969).
(6) M. S. Gibson and M. Green, *Tetrahedron*, **21**, 2191 (1965).
(7) E. H. Wolf and B. J. Duffy, Abstracts, 170th National Meeting of the American Chemical Society, Chicago, Ill., Aug 25–29, 1975, No. ORGN-97.
(8) A. L. Langis and M. P. Charest, *Chim. Ther.*, 349 (1967).
(9) (a) M. Takahashi, S. Onizawa, and T. Satoh, *Bull. Chem. Soc. Jpn.*, **47**, 2724 (1974). (b) The product of the reaction of isatoic anhydride with 2-pyridylamidrazone is 2-aminobenzoic acid 2-[(imino-2-pyridyl)methyl]hydrazide.
(10) The isatoic anhydride (mp 243–247 °C dec, colorless prisms) used in this reaction was prepared as described by N. P. Peet and S. Sunder, *J. Org. Chem.*, **39**, 1931 (1974), from methyl anthranilate.
(11) We are indebted to Dr. R. L. Jacobs of Sherwin-Williams Chemicals for suggesting these reaction conditions in a private communication.
(12) The mixture of hydrazides **2** and **3** (85:15, respectively) was used in this reaction. Yield is based on the total weight of the starting mixture.
(13) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds", 2d ed, Wiley, New York, N.Y., 1967, p 162.
(14) Melting points are uncorrected. Ir spectra were recorded with a Perkin-Elmer 727B instrument; NMR spectra with Varian T-60 and Perkin-Elmer R32 (90 MHz) spectrometers; uv spectra with a Cary 15 spectrophotometer; mass spectra with a Hitachi RMU-6D mass spectrometer. Combustion analyses were performed by Dow Analytical Laboratories.
(15) The position of the NCH_3 group assigned to **3** was identical with that found for an authentic sample of **3,** whose synthesis will be described in a future report.[3c] The 85:15 mixture of hydrazides **2** and **3** was also substantiated by VPC analysis (5 ft × 0.125 in. 5% SE-30, 225 °C, 30 ml/min of He) where **2** eluted at 1.7 min and **3** at 2.3 min. Coinjection of this mixture with authentic **3** enhanced the peak at 2.3 min.
(16) Another paper by R. W. Leiby and N. D. Heindel, describing compounds **5a, b,** and **d,** appears in this issue.

Preparation and Utility of 1-Acetyl-1-methylhydrazine

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An efficient, simple synthesis of 1-acetyl-1-methylhydrazine (**1**) from acetyl chloride and methylhydrazine is reported. The utility of this protected methylhydrazine unit is demonstrated by the preparation of 1-methyl-4-phenylsemicarbazide (**5**) and 2-(o-nitrobenzoyl)-1-methylhydrazine (**14**). 2-(o-Aminobenzoyl)-1-acetyl-1-methylhydrazine (**9**), which was prepared either from **1** and isatoic anhydride (**10**) or from **1** and *o*-nitrobenzoyl chloride (**7**) followed by reduction, was cyclized to 2-methyl-3-(methylamino)-4(3*H*)-quinazolinone (**11**) with 10% sulfuric acid. The mechanism of this transformation, which demonstrates the utility of **1** in heterocyclic synthesis, is discussed.

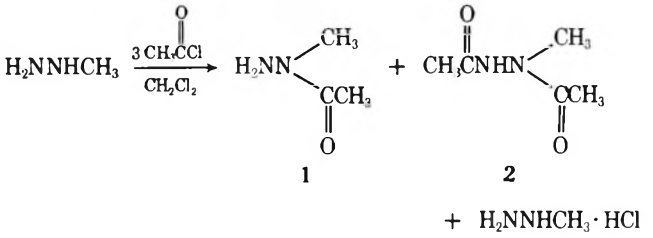
1-Acetyl-1-methylhydrazine has been prepared from the monoacetylhydrazone of 2,3-butanedione by methylation of the potassium salt with methyl iodide and subsequent hydrolysis.[1] (An earlier report,[2] describing 1-acetyl-1-methylhydrazine as a solid, mp 98 °C, as the product from this same synthetic procedure is in error.) This three-step synthesis is cumbersome and the overall yield is poor.

A more recent procedure[3] describes the preparation of 1-acetyl-1-methylhydrazine from methylhydrazine and acetic anhydride in acetic acid (99% purity in 46% yield) or pyridine (96% purity in 76% yield). These procedures suffer the disadvantages of requiring specialized equipment, specific temperature monitoring, a long reaction time, a neutralization step which produces troublesome sodium acetate trihydrate, and extractions with a toxic solvent (pyridine). Distillation of the crude product is also troubled by the presence of pyridine, water, methylhydrazine, and a significant amount of unidentified white solid. These drawbacks are obviated by the following procedure, which is exceedingly simple.

A methylene chloride solution of acetyl chloride was added to a rapidly stirring solution of 3 equiv of methylhydrazine in methylene chloride. The methylhydrazine hydrochloride was

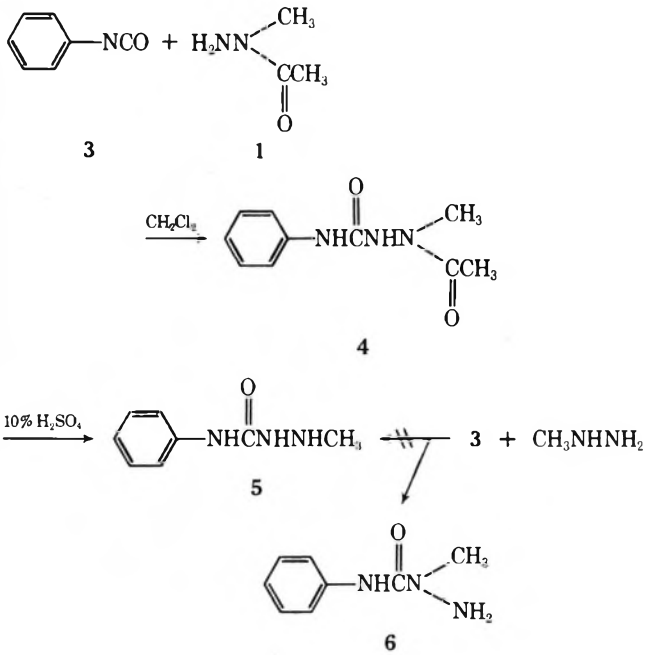
removed by filtration and the concentrated filtrate distilled under reduced pressure to yield 60–65% of pure 1-acetyl-1-methylhydrazine (1). A second fraction could be obtained which yielded 25–29% of (crude) 1,2-diacetylmethylhydrazine (2). See Scheme I.

Scheme I



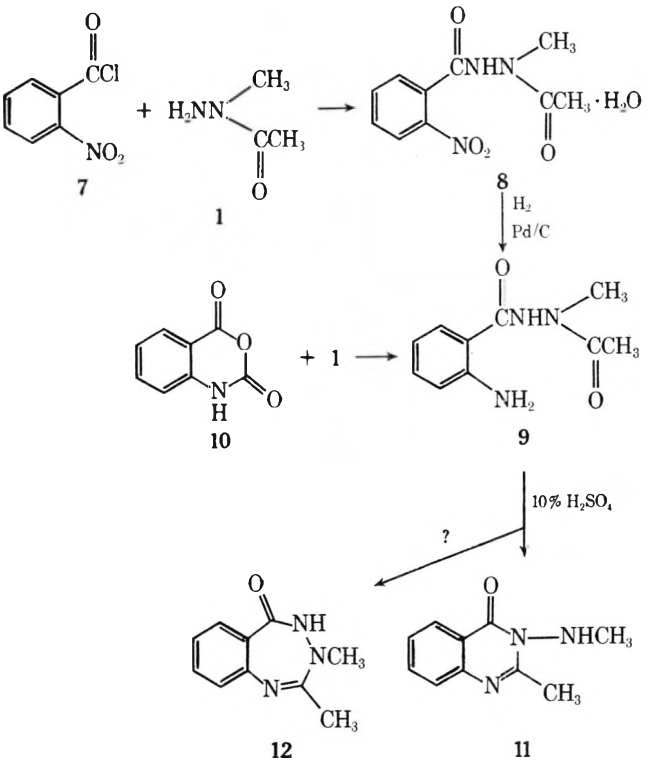
The methyl-bearing nitrogen of methylhydrazine has been shown to selectively attack reactive functional groups such as carboxylic acid anhydrides[3,4] and chlorides,[5] isocyanates,[5,6] and isothiocyanates.[6] By acylating the methyl-bearing nitrogen of methylhydrazine, a derivative is produced which can react only by nucleophilic attack of the primary amino nitrogen. Thus, we were able to produce 1-acetyl-1-methyl-4-phenylsemicarbazide (4) in 86% yield from the reaction of 1 with phenyl isocyanate (3). The acetyl group was cleanly removed by hydrolysis with 10% sulfuric acid to yield 1-methyl-4-phenylsemicarbazide (5), isomeric with 2-methyl-4-phenylsemicarbazide (6), which is the sole product obtained from the reaction of methylhydrazine with 3.[7,8] See Scheme II.

Scheme II



In exploring the utility of 1-acetyl-1-methylhydrazine (1) in heterocyclic syntheses, we treated *o*-nitrobenzoyl chloride (7) with 1, as shown in Scheme III. Catalytic reduction of the resulting 2-(*o*-nitrobenzoyl)-1-acetyl-1-methylhydrazine monohydrate (8) produced the corresponding aniline 9, which could also be prepared from isatoic anhydride (10) and 1. Treatment of 9 with 10% sulfuric acid led to a new compound, from net dehydration. At this point we suspected that the new material was 2-methyl-3-(methylamino)-4(3*H*)-quinazolinone

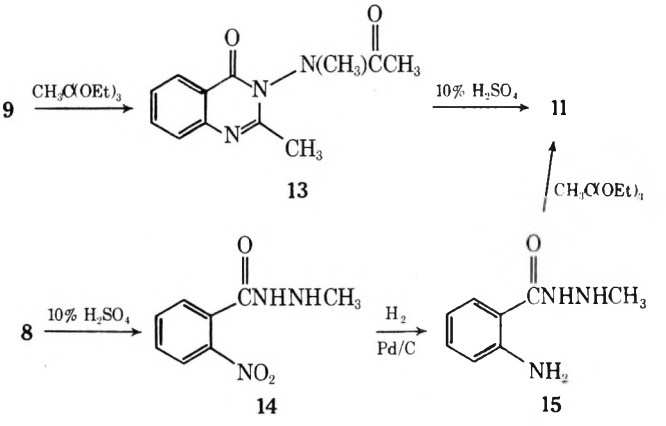
Scheme III



(11), but we could not rule out the possibility of the interesting benzotriazepinone 12.

To establish the structure of this new product we synthesized authentic 11 by the routes shown in Scheme IV. Com-

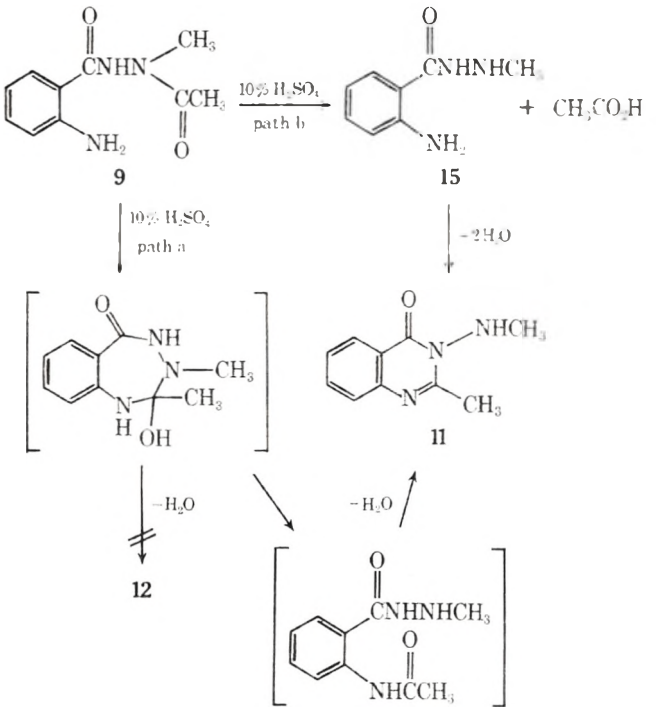
Scheme IV



pound 9 was cyclized with triethyl orthoacetate to yield *N*-methyl-*N*-[2-methyl-4-oxo-3(4*H*)-quinazolinyl]acetamide (13). Subsequent hydrolysis with 10% sulfuric acid produced 11. Alternatively, 8 was hydrolyzed with 10% sulfuric acid to 2-(*o*-nitrobenzoyl)-1-methylhydrazine (14), which was catalytically reduced to 2-(*o*-aminobenzyl)-1-methylhydrazine (15).[10] Hydrazide 15 was then cyclized to 11 with triethyl orthoacetate. Quinazolinone 11, made by the routes shown in Scheme IV, was identical with the product obtained from the treatment of 9 with sulfuric acid (Scheme III).

Two possible mechanisms for the conversion of diacylhydrazine 9 to quinazolinone 11 are depicted in Scheme V. Path a involves the initial transfer of the acetyl moiety to the aromatic amino group via a hydroxybenzotriazepinone to afford 2-[*o*-(acetylamino)benzoyl]-1-methylhydrazine, which should readily cyclodehydrate under acidic conditions to give 11.

Scheme V



Alternatively, we considered path b, in which hydrolysis produces hydrazide **15** and acetic acid, which then might condense to form **11**. However, when we treated hydrazide **15** with 1 equiv of acetic acid and 10% sulfuric acid, we isolated only unchanged **15**. We, therefore, favor the mechanism depicted in path a.

The use of 1-acetyl-1-methylhydrazine (**1**) in the preparation of 2-alkyl-1-methylhydrazines is documented.[3,12] A future report from our laboratory will include additional utility of **1** in heterocyclic synthesis.

Experimental Section[13]

Reaction of Acetyl Chloride with Methylhydrazine.[14] To an efficiently stirred solution of 138 g (3.00 mol) of methylhydrazine (Aldrich) in 800 ml of CH_2Cl_2 was added a 78.5-g (1.00 mol) quantity of acetyl chloride (Mallinckrodt) in 250 ml of CH_2Cl_2 over a 30-min period with ice-bath cooling.[15] After 30 min of stirring at room temperature the white solid was removed by filtration and washed with CH_2Cl_2.[16] Evaporation of the filtrate left 80–85 g of clear oil, which was distilled in two major fractions.[17] After a 1–2-g forerun, the first fraction yielded 53–57 g (60–65%) of 1-acetyl-1-methylhydrazine (**1**): bp 75–79 °C (0.60 mm) [lit.[3] bp 103 °C (8 mm)]; n^{25}D 1.4677; ir (neat) 3330 and 3230 (NH), 1640 cm^{-1} (broad, C=O); NMR ($CDCl_3$) δ 4.25 (s, 2, NH_2, D_2O exchangeable), 3.20 and 3.14 (2 singlets, 3, NCH_3), 2.17 and 2.07 (2 singlets, 3, $COCH_3$);[18] mass spectrum (70 eV) *m/e* 88 (molecular ion); VPC analysis (8 ft × 0.125 in., 5% SE-30, 125 °C, 30 ml/min of He) showed a single peak at 1.6 min.

Anal. Calcd for $C_3H_8N_2O$: C, 40.89; H, 9.15; N, 31.80. Found: C, 40.70; H, 8.94; N, 31.64.

Complete distillation of the first fraction was signaled by a head-temperature drop, and an intermediary fraction of viscous, yellow oil (3–4 g) was collected. The second fraction was collected as a clear or yellow liquid which codistilled with a small amount of white solid, and yielded 16–19 g (25–29%) of crude 1,2-diacetylmethylhydrazine (**2**). The distillate was purified by elution through a short column of alumina (Fisher A-540) with CH_2Cl_2. The eluent was concentrated and redistilled to afford 12–16 g (18–25%) of pure **2**:[20] bp 164 °C (1.10 mm); n^{25}D 1.4666; ir (neat) 3250 (broad NH), 167 cm^{-1} (broad C=O); NMR ($CDCl_3$) δ 9.37 (s, 1, NH, D_2O exchangeable), 3.07 (s, 3, NCH_3), 2.03 (s, 6, both CH_3CO groups); mass spectrum (70 eV) *m/e* 131 (molecular ion). VPC analysis (8 ft × 0.125 in., 5% SE-30, 225 °C, 30 ml/min of He) showed a single peak at 1.6 min.

Anal. Calcd for $C_5H_{10}N_2O_2$: C, 46.14; H, 7.75; N, 21.53. Found: C, 45.90; H, 7.58; N, 21.35.

1-Acetyl-1-methyl-4-phenylsemicarbazide (4). To a solution of 11.9 g (0.100 mol) of phenyl isocyanate (Aldrich) in 50 ml of CH_2Cl_2 was added a solution of 8.81 g (0.100 mol) of **1** in 25 ml of CH_2Cl_2 with ice-bath cooling. The resulting white solid was collected and washed with ether to yield 17.9 g (86%) of **4** (mp 156–158 °C): mp 163–164 °C (EtOH); ir (Nujol) 3300, 3200, 3150 and 3100 (NH), 1660 cm^{-1} (broad C=O); NMR (Me_2SO-d_6) δ 8.95 (broad s, 1, NH, D_2O exchangeable), 8.60 (broad s, 1, NH, D_2O exchangeable), 7.58–6.71 (m, 5, aromatic), 3.00 (s, 3, NCH_3), 1.97 (s, 3, $COCH_3$).

Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.00; H, 6.16; N, 20.17.

1-Methyl-4-phenylsemicarbazide (5). A 4.00-g (19.3 mmol) quantity of **4** was mixed with 50 ml of 10% H_2SO_4 and warmed gently (5 min) until solution resulted. After 10 min at room temperature, the solution was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried (Na_2SO_4) and concentrated to yield 0.82 g (21%) of recovered **4**. The aqueous phase was basified with NaOH, extracted with CH_2Cl_2, and the extracts were dried (Na_2SO_4) and concentrated to yield 1.98 g (62%) of **5**: mp 107–108 °C (EtOH) (lit.[7c] mp 102–104 °C); ir (Nujol) 3350 (s), 3280 (s), and 3250 (NH), 1675, 1640 cm^{-1}; NMR ($CDCl_3$) δ 8.10 (broad s, 1, NH), 7.50–6.75 (m, 5, aromatic), 6.60 (broad s, 1, NH), 3.60 (broad s, 1, NH), 2.60 (s, 3, CH_3).

Anal. Calcd for $C_8H_{11}N_3O$: C, 58.16; H, 6.71; N, 25.44. Found: C, 57.90; H, 6.70; N, 25.22.

2-(*o*-Nitrobenzoyl)-1-acetyl-1-methylhydrazine Monohydrate (8). To a solution of 21.0 g (0.113 mol) of *o*-nitrobenzoyl chloride (Aldrich) in 100 ml of CH_2Cl_2 was added 19.9 g (0.226 mol) of **1** in 25 ml of CH_2Cl_2 with ice-bath cooling. After 1 h, 100 ml of water was added and a heavy precipitate formed. The precipitate was collected and air dried to yield 18.5 g (64%) of **8**: mp 106–108 °C (EtOH); ir (Nujol) 3440–3170 (NH and H_2O), 1670, 1640 cm^{-1}; NMR (Me_2SO-d_6) δ 11.00 (s, 1, NH), 8.20–8.00 (m, 1, H ortho to C=O), 8.00–7.60 (m, 3, remaining aromatic), 3.50 (s, 2, H_2O), 3.08 (s, 3, NCH_3), 2.02 (s, 3, $COCH_3$).

Anal. Calcd for $C_{10}H_{13}N_3O_5$: C, 47.06; H, 5.13; N, 16.47. Found: C, 47.00; H, 5.10; N, 16.53.

2-(*o*-Aminobenzoyl)-1-acetyl-1-methylhydrazine (9). A. From 8. A 4.00-g (15.7 mmol) quantity of **8** in 40 ml of EtOH was hydrogenated in a Parr apparatus at 50 psi of hydrogen in the presence of 10% Pd/C (400 mg) for 2 h. Uptake of hydrogen (3.5 lb) was essentially complete after 10 min. The catalyst was removed by filtration and the filtrate was concentrated to a small volume. The white prisms which formed were collected and washed with ether to yield 2.60 g (80%) of **9**: mp 147–148.5 °C; ir (Nujol) 3480 (s), 3360 (s), and 3280 (NH), 1660 cm^{-1} (both C=O groups); NMR ($CDCl_3$ + Me_2SO-d_6) δ 10.37 (s, 1, NH, D_2O exchangeable), 7.48–7.34 (m, 1, H ortho to C=O), 7.27–6.97 (m, 1, H para to C=O), 6.78–6.38 (m, 2, remaining aromatic), 5.88 (broad s, 2, NH_2, D_2O exchangeable), 3.30 and 3.14 (2 singlets in 1:10 ratio, respectively, NCH_3), 2.15 and 2.03 (2 singlets in 1:10 ratio, respectively, $COCH_3$).

Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.00; H, 6.39; N, 20.28.

B. From Isatoic Anhydride (10). An 11.8-g (72.3 mmol) quantity of isatoic anhydride[21] and 6.37 g (72.3 mmol) of **1** were mixed together and heated on a steam bath until CO_2 evolution ceased. The viscous oil was dissolved in a minimal volume of EtOH, a seed crystal was added, and the solution was cooled overnight in a freezer. The next morning, the white solid was collected to yield 4.48 g (30%) of **9**, mp 148.5–149.5 °C, whose ir (Nujol) was identical with that of the material prepared in part A.

***N*-Methyl-*N*-[2-methyl-4-oxo-3(4*H*)-quinazolinyl]acetamide (13).** A 4.20-g (20.0 mmol) quantity of **9** in 20 ml of triethyl orthoacetate (Aldrich) was heated at reflux for 12 h. The solution was concentrated to dryness, the resulting solid was slurried with hot EtOH and cooled, and the product was collected to yield 3.00 g (64%) of **13**: mp 148–149 °C; ir (Nujol) 1690, 1670 cm^{-1}; NMR ($CDCl_3$) δ 8.37–8.14 (m, 1, H ortho to C=O), 8.00–7.34 (m, 3, remaining aromatic), 3.50 and 3.34 (2 singlets in a 1:3 ratio, respectively, NCH_3), 2.59 and 2.48 (2 singlets in a 3:1 ratio, respectively, CCH_3), 2.36 and 1.92 (2 singlets in a 1:3 ratio, respectively, $COCH_3$).

Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.33; H, 5.74; N, 18.19.

2-(*o*-Nitrobenzoyl)-1-methylhydrazine (14). A 10.0-g (39.2 mmol) quantity of **8** was slurried with 50 ml of 10% H_2SO_4, warmed on a hot plate until solution resulted, and then warmed at 80 °C for an additional 25 min. The solution was cooled, neutralized, and made slightly basic with NaOH. The resulting precipitate was collected and air dried to yield 6.20 g (81%) of **14**: mp 130–131 °C (EtOH); ir (Nujol) 3275 (NH), 1640 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.17–7.90 (m, 1, aromatic), 7.70–7.32 (m, 3, aromatic), 4.47 (broad s, 2, both NH groups, D_2O exchangeable), 2.64 and 2.47 (2 singlets in a 3:1 ratio, respectively, NCH_3).

Anal. Calcd for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.10; H, 4.60; N, 21.66.

2-(*o*-Aminobenzoyl)-1-methylhydrazine (15). A 4.00-g (20.5 mmol) quantity of **14** in 40 ml of EtOH was hydrogenated in a Parr apparatus at 50 psi of hydrogen in the presence of 10% Pd/C (400 mg) for 90 min. Uptake of hydrogen (4 lb) was essentially complete after 10 min. The catalyst was removed by filtration and the filtrate was concentrated and triturated with ether. The resulting solid was collected to yield 3.00 g (89%) of **15** (mp 85–87 °C): mp 90–91 °C (hexane); ir (Nujol) 3430 and 3300 (NH), 1620 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.34–6.90 (m, 2, aromatic), 6.66–6.32 (m, 2, aromatic), 5.50 (broad s, 4, both NH groups and NH_2), 2.63 (s, 3, CH_3).

Anal. Calcd for $C_8H_{11}N_3O$: C, 58.16; H, 6.71; N, 25.44. Found: C, 57.90; H, 6.56; N, 25.23.

2-Methyl-3-(methylamino)-4(3*H*)-quinazolinone (11). A. From 9. A 1.00-g (4.83 mmol) quantity of **9** was mixed with 20 ml of 10% H_2SO_4, warmed on a hot plate until solution resulted, and then warmed at 80 °C for an additional 30 min. The solution was cooled, basified with NaOH, and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated to yield 710 mg (78%) of **11**: mp 110–111 °C (EtOH); ir (Nujol) 3300 (NH) and 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.31–8.10 (m, 1, H ortho to C=O), 7.81–7.24 (m, 3, remaining aromatic), 5.78 (q, J = 6 Hz, 1, NH), 2.81 (d, J = 6 Hz, 3, NCH_3), 2.71 (s, 3, CCH_3). When the NMR sample was shaken with D_2O, the NH signal at δ 5.78 disappeared and the NCH_3 doublet at δ 2.81 collapsed to a singlet at δ 2.81; mass spectrum (70 eV) *m/e* 189 (molecular ion).

Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.60; H, 5.85; N, 22.07.

B. From 13. A 1.00-g (4.32 mmol) quantity of **13** was mixed with 10 ml of 10% H_2SO_4 and heated at 80–90 °C for 1 h. The solution was cooled, basified with NaOH, and extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated to afford 480 mg (59%) of crude **11**, mp 97–99 °C, whose ir (Nujol) was identical with that of the material prepared in part A.

C. From 15. A 1.00-g (4.83 mmol) quantity of **15** in 20 ml of triethyl orthoacetate was heated at reflux for 12 h. The solution was concentrated and the resulting solid was crystallized (EtOH) to afford 450 mg (49%) of pure **11**, mp 110–111 °C, whose ir (Nujol) was identical with that of the material prepared in part A.

Registry No.—**1**, 3530-13-0; **2**, 38604-72-7; **3**, 931-54-4; **4**, 5790-59-0; **5**, 40028-55-5; **7**, 610-14-0; **8**, 59169-42-5; **9**, 59169-43-6; **10**, 118-48-9; **11**, 59169-44-7; **13**, 59169-45-8; **14**, 59169-46-9; **15**, 59169-47-0; methylhydrazine, 60-34-4; acetyl chloride, 75-36-5; methylhydrazine HCl, 7339-53-9; triethyl orthoacetate, 78-39-7.

References and Notes

(1) K. Ronco and H. Erlenmeyer, *Helv. Chim. Acta*, **39**, 1045 (1956).
(2) O. Diels and A. V. Dorp, *Ber.*, **36**, 3189 (1903).
(3) F. E. Condon, *J. Org. Chem.*, **37**, 3608 (1972).
(4) A. R. McCarthy, W. D. Ollis, A. N. M. Barnes, L. E. Sutton, and C. Ainsworth, *J. Chem. Soc. B*, 1185 (1969).
(5) N. P. Peet and S. Sunder, *J. Org. Chem.*, **40**, 1909 (1975).
(6) M. Busch, E. Opfermann, and H. Walther, *Ber.*, **37**, 2318 (1904).
(7) (a) M. Wilcox, *J. Med. Chem.*, **11**, 171 (1968); (b) French Patent 1 521 959 (1968); *Chem. Abstr.*, **71**, 3166k (1969); (c) G. Zinner and K. Dorschner, *Arch. Pharm. (Weinheim, Ger.)*, **306**, 35 (1973).
(8) 1-Methyl-4-phenylsemicarbazide (hydrochloride) has been prepared using less direct methods than the one described in Scheme II. 2-Phenyl-3-methyl-5-(phenyl)amino-1,3,4-oxadiazolium chloride, which was prepared from 1-benzoyl-1-methylhydrazine and phenyl isocyanide dichloride, was decomposed in methanol solution to yield **5** HCl.[9a] In addition, 1-methyl-3,3-pentamethylenediaziridine, prepared either from cyclohexanone, ammonia, and methylhydroxylamine-*O*-sulfonic acid or cyclohexanone, methylamine, and hydroxylamine-*O*-sulfonic acid,[9b] was reacted with phenyl isocyanate and subsequently hydrolyzed to **5**.[7c] In both of these syntheses, as in ours, the methylhydrazine derivative employed to introduce the methylhydrazine unit was one in which the *N*-methyl nitrogen was protected.
(9) (a) W. D. Ollis and C. Ramsden, *Chem. Commun.*, 1223 (1971); (b) E. Schmitz, R. Ohme, and R. D. Schmidt, *Chem. Ber.*, **95**, 2714 (1962).
(10) A mixture of hydrazide **15** and 1-(*o*-aminobenzoyl)-1-methylhydrazine were produced in a 15:85 ratio, respectively, by the reaction of isatoic anhydride with methylhydrazine in DMF. The authentic sample of **15** produced as shown in Scheme IV was used to identify its presence in the mixture.[11]
(11) S. Sunder, N. P. Peet, and D. L. Trepanier, *J. Org. Chem.*, preceding paper in this issue.
(12) F. E. Condon, *J. Org. Chem.*, **37**, 3615 (1972).
(13) Melting points are uncorrected. Ir spectra were recorded with a Perkin-Elmer 727B instrument; NMR spectra with a Varian T-60 spectrometer; and mass spectra with a Hitachi RMU-6D mass spectrometer. Combustion analyses were performed by Dow Analytical Laboratories.
(14) The procedure described is based on several reactions.
(15) The atmosphere in the reaction vessel is foggy during the addition. Vigorous stirring during the addition appears to increase the ratio of monoacylated to diacylated product. Midway through the addition a white precipitate is observed.
(16) The dried, white, crystalline solid is methylhydrazine hydrochloride, (mp 78–79.5 °C), weighing 80–82 g. and is analytically pure. Anal. Calcd for CH_7ClN_2: C, 14.55; H, 8.54; N, 33.93. Found: C, 14.50; H, 8.49; N, 34.28.
(17) The separation is easily effected with a 1 × 10 cm vacuum-jacketed Vigreux column (ca. three theoretical plates).
(18) The NMR spectrum of **1** indicated the presence of two conformers, with the inside, slightly more intense, set of singlets belonging to the methyl groups of one rotamer and the outside set to the methyl groups of the other. An NMR study on the conformer proportions of 1-acetyl-1-methylhydrazine in polar and nonpolar solvents is reported.[19] The NMR spectrum also indicated the absence of significant amounts of 1-acetyl-2-methylhydrazine, whose NMR spectrum ($CDCl_3$) is recorded.[3]
(19) P. Bouchet, J. Elquero, R. Jacquier, and J. M. Pereillo, *Bull. Soc. Chim. Fr.*, 2264 (1972).
(20) 1,2-Diacetylmethylhydrazine (bp 280 °C) has been prepared by reacting methylhydrazine with excess acetic anhydride: A. Michaelis and E. Hadanck, *Ber.*, **41**, 3285 (1908).
(21) The isatoic anhydride (mp 243–247 °C dec, colorless prisms) used in this reaction was prepared as described by N. P. Peet and S. Sunder, *J. Org. Chem.*, **39**, 1931 (1974), from methyl anthranilate.

Synthesis of 3,4-Dihydro- and 1,4-Dihydro-5*H*-1,3,4-benzotriazepin-5-ones

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2-Aminobenzoic acid 1-methylhydrazides (**1**) react with ortho esters to yield 3,4-dihydro-(**2a–o**) and 1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (**3a–h**). Proton magnetic resonance studies were employed to define the predominant tautomer in the tautomeric members of the benzotriazepine class.

The synthetic interest in benzodiazepines arising from their well-established role as potential psychotherapeutics has prompted investigations into their nitrogen homologues, the benzotriazepines. Several studies have reported the preparation of members of the 1,3,4-benzotriazepine family[1–6] but the synthetic methods were not unambiguous and could easily have generated isomeric five- or six-membered heterocyclics. In fact, several of these earlier syntheses were recently called into question and the alternate structures established.[7]

The availability of authentic 2-aminobenzoic acid 1-methylhydrazides[8] ensures that cyclization with a one carbon insertion unit will involve the ortho amino and the β nitrogen

Table I. 2-Aminobenzoic Acid 1-Methylhydrazides

Registry no.	Compd	X	R	Yield, %	Bp, °C (mm) (mp, °C)	Formula	Anal.[a]
59169-69-6	1a[b]	H	H	84.5	154–155 (0.35)	$C_8H_{11}N_3O$	CHN
59169-70-9	1b[b]	Cl	H	82.5	162–163 (0.20)	$C_8H_{10}ClN_3O$	CHN
59169-71-0	1c	Br	H	67.3	(100.0–100.5)[c]	$C_8H_{10}BrN_3O$	CHN
59169-72-1	1d	NO_2	H	69.5	(160.0–160.5)[d]	$C_8H_{10}N_4O_3$	CHN
59169-73-2	1e[b]	H	CH_3	86.0	157–158 (0.80)	$C_9H_{13}N_3O$	CHN
59169-74-3	1f	Cl	CH_3	81.2	160–163 (0.07)	$C_9H_{12}ClN_3O$	CH
59169-75-4	1g	NO_2	CH_3	58.0	(189.0–189.5)[d]	$C_9H_{12}N_4O_3$	CHN

[a] Analytical data were within ±0.3% for indicated elements. Ed. [b] Previously reported: R. W. Leiby and N. D. Heindel, *Synth. Commun.*, in press. [c] Recrystallized from 95% ethanol. [d] Recrystallized from dioxane.

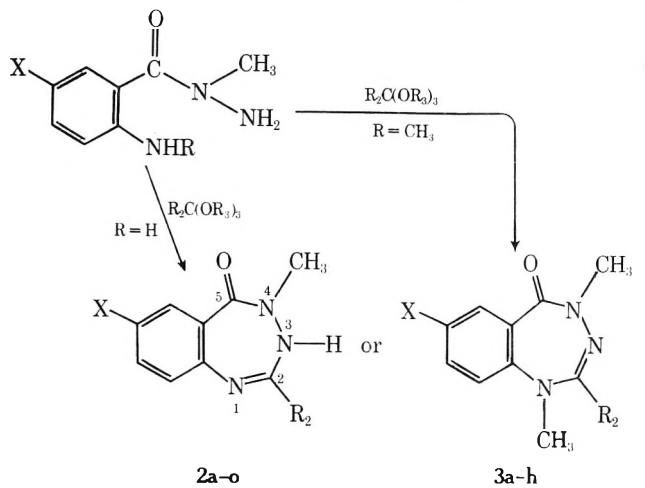
Table II. Benzotriazepinones[a]

Registry no.	Compd	X	R_2	Yield, %	Mp, °C	Formula
59169-76-5	2a	H	H	89	162.0–162.5	$C_9H_9N_3O$
59169-77-6	2b	Cl	H	72	222.0–223.5	$C_9H_8ClN_3O$
59169-78-7	2c	Br	H	73	256.5–257.0	$C_9H_8BrN_3O$
59169-79-8	2d	NO_2	H	71	270.5–271.0	$C_9H_8N_4O_3$
59169-80-1	2e	H	CH_3	58	133.0–133.5	$C_{10}H_{11}N_3O$
59169-81-2	2f	Cl	CH_3	61	227–228	$C_{10}H_{10}ClN_3O$
59169-82-3	2g	Br	CH_3	58	226–227	$C_{10}H_{10}BrN_3O$
59169-83-4	2h	NO_2	CH_3	84	277–278	$C_{10}H_{10}N_4O_3$
59169-84-5	2i	Cl	C_2H_5	68	167–168	$C_{11}H_{12}ClN_3O$
59169-85-6	2j	Br	C_2H_5	46	176.0–176.5	$C_{11}H_{12}BrN_3O$
59169-86-7	2k	NO_2	C_2H_5	85	203–205	$C_{11}H_{12}N_4O_3$
59169-87-8	2l	H	C_6H_5	68	165–166	$C_{15}H_{13}N_3O$
59169-88-9	2m	Cl	C_6H_5	64	240–241	$C_{15}H_{12}ClN_3O$
59169-89-0	2n	Br	C_6H_5	51	247–248	$C_{15}H_{12}BrN_3O$
59169-90-3	2o	NO_2	C_6H_5	69	295–296	$C_{15}H_{12}N_4O_3$
59169-91-4	3a	H	H	53	102.5–103.5	$C_{10}H_{11}N_3O$
59169-92-5	3b	Cl	H	61	166.0–166.5	$C_{10}H_{10}ClN_3O$
59169-93-6	3c	NO_2	H	57	225–227	$C_{10}H_{10}N_4O_3$
59169-94-7	3d	H	CH_3	77	150.5–151.5	$C_{11}H_{13}N_3O$
59169-95-8	3e	Cl	CH_3	64	131–132	$C_{11}H_{12}ClN_3O$
59169-96-9	3f	NO_2	CH_3	44	185.5–186.0	$C_{11}H_{12}N_4O_3$
59169-97-0	3g	NO_2	C_2H_5	42	149.5–150.0	$C_{12}H_{14}N_4O_3$
59169-98-1	3h	Cl	C_6H_5	27	104.0–105.5	$C_{16}H_{14}ClN_3O$

[a] Analytical data were within ±0.3% for C, H, N. Ed. All components were recrystallized from ethanol except 3c, which was sublimed in vacuo, and 2o, which was recrystallized from dioxane.

of the hydrazide and produce a benzotriazepine. Treatment of these substituted 2-aminobenzoic acid 1-methylhydrazides (**1a–g**) (see Table I) with ortho esters resulted in 3,4-dihydro- (**2a–o**) and 1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (**3a–h**) (Scheme I).

Scheme I[a]



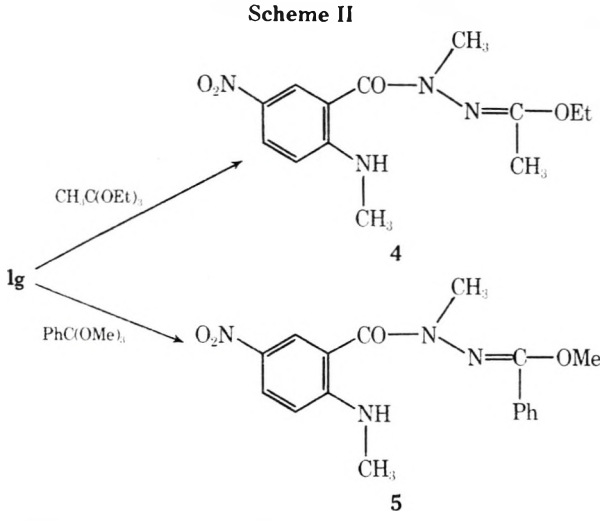
2a–o **3a–h**

[a] Ortho esters employed were triethyl orthoformate, triethyl orthoacetate, triethyl orthopropionate, and trimethyl orthobenzoate.

Although the hydrazides normally yield the benzotriazepines directly, it appears that the stepwise mechanism for the cyclization involves initial condensation with the more nucleophilic hydrazide nitrogen with subsequent closure by the anilino nitrogen on the ortho ring position. In **1g** the reduced nucleophilicity of the ortho amino and a degree of steric hindrance imparted by the *N*-methylamino substituent and the choice of ortho ester permitted the isolation of two noncyclized adducts. Reaction of 2-methylamino-5-nitrobenzoic acid 1-methylhydrazide (**1g**) with triethyl orthoacetate and trimethyl orthobenzoate was found to give 2-methylamino-5-nitrobenzoic acid 2-*N*-(1-ethoxy)ethylidene-1-*N*-methylhydrazide (**4**) and 2-methylamino-5-nitrobenzoic acid 2-*N*-(1-methoxy)benzylidene-1-*N*-methylhydrazide (**5**), respectively (Scheme II). In addition to the orthoacetate intermediate (**4**), the benzotriazepine (**3f**) was also isolated. These compounds displayed characteristic N–H absorbances at 3380 cm^{-1} and strong C–O ether absorptions at 1300 cm^{-1} in the infrared. The ^1H NMR spectra displayed the 2-methylamino methyl protons as doublets and the corresponding amine protons as quartets. The expected resonances for the ethoxy and methoxy groups were also present in the respective ^1H NMR spectral data.

Assignment of the potentially tautomeric nitrogen–carbon double bond in the benzotriazepines **2a–o** can be made by spectral comparisons with model compounds. Benzotriazepines **3a–h** derived from the 2-*N*-methylaminobenzoic acid hydrazides, with the unsaturation at C_2–N_3, show N_4-methyl

Scheme II

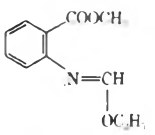


resonances at δ 3.32 ± 0.06 ppm whereas the corresponding methyl signal appears at 3.14 ± 0.05 in the noncyclic *N*-2-methylaminobenzoic acid hydrazide precursors. In **4** and **5** the hydrazide *N*-methyl signal was located at 3.30 ppm. The downfield shift of approximately 10 Hz which was observed for the N_4-methyl resonance in each compound is in accord with the expected additional deshielding provided by the adjacent C_2–N_3 double bond.

The benzotriazepines (**2a–o**) prepared from the 2-aminobenzoic acid hydrazides might be 3,4-dihydro or 1,4-dihydro tautomers. The assignment as 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones **2** is based on the position of their N_4-methyl signals (3.19 ± 0.06 ppm) compared to those in the noncyclic hydrazide precursors (3.14 ± 0.05 ppm). This deshielding presumably arises from the more rigid geometry in the heterocyclic product which constrains the NCH_3 to the nodal plane of the hydrazide carbonyl. In earlier studies on the cyclization of *N*-methylanthranilamides to quinazolinones[9] we observed a similar downfield shift of the amidic *N*-methyl of approximately 3 Hz in the cyclized product compared to the acyclic precursor. Much greater deshielding of the N_4-methyl resonance in the benzotriazepines would be expected if the tautomeric double bond localized at the C_2–N_3 locus.

Ultraviolet spectra (see Table III) of a fixed bond isomer (**3a**), a potentially tautomeric compound (**2a**), and a synthetic

Table III. Ultraviolet Spectral Data

Compd	λ, nm	Log ε
2a	331	2.76
	282	3.63
	251	4.28
	233	4.47
3a	320	2.86
	278	3.70
	257	4.15
	237	4.40
	338	3.62
	312	3.72
	253	4.14
	227	4.62

6

model with imino unsaturation at the ortho-amino function (**6**) also indicate the N_1–C_2 tautomer. Not only does **2a** have a longer λ_{max} (in accord with the expected benzenoid overlap of its potential N_1–C_2 unsaturation), but it also displays a closer spectral similarity to the imino model than does **3a**.

Experimental Section

Infrared spectra were obtained in KBr on a Perkin-Elmer 257 spectrophotometer. A Hitachi Perkin-Elmer R20A nuclear magnetic resonance spectrometer was employed to obtain the ^1H NMR spectra. Combustion analyses were provided by Dr. G. I. Robertson, Florham Park, N.J.

Preparation of 2-Aminobenzoic Acid 1-Methylhydrazides (1). The ring opening of isatoic anhydrides by methylhydrazine to yield **1a, 1b,** and **1e** was described in a publication from these laboratories.[8] Additional compounds obtained by this route are listed in Table I.

Preparation of Benzotriazepinones 2a–o and 3a–h. The requisite benzoic acid hydrazide (**1a–g**) was suspended in a 25% excess of an orthoester and stirred at reflux until solution resulted. Heating and stirring were continued for an additional 4 h unless precipitation of solid terminated the agitation. After chilling of the reaction mixture the crystals were filtered, washed quickly with cold ether, and recrystallized from ethanol (properties and exceptions are noted in Table II). The nitrobenzoic acid hydrazide (**1g**) required modified reaction conditions and cyclization was considerably less facile.

7-Nitro-1,2,4-trimethyl-1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (3f) and 2-Methylamino-5-nitrobenzoic Acid 2-*N*-(1-Ethoxyethylidene)-1-*N*-methylhydrazide (4). 2-Methylamino-5-nitrobenzoic acid 1-methylhydrazide (**1g,** 11.22 g, 0.050 mol) was added to 40 ml of 2-methoxyethyl ether. The mixture was heated to reflux, whereupon solution occurred. To the refluxing solution was then dropwise added, over a period of 30 min, 8.50 g (0.050 mol) of triethyl orthoacetate. After 20 h, refluxing was terminated, and while still warm, the solution was concentrated in vacuo. The viscous liquid which resulted was stirred vigorously in ether, to induce crystallization. The solid was lixiviated with ether. Evaporation of the ether gave **4** as a yellow solid. Recrystallization of the product from ether afforded 1.85 g (15%) of **4** as fine needles: mp 127.0–127.5 °C; ir (KBr) 3380 (N–H), 1660 (shoulder C=O), 1610 (C=N), 1320 cm^{-1} (C–NO_2); NMR ($CDCl_3$) δ 1.21 (t, 3, CH_2CH_3), 1.87 [s, 3, N=C(CH_3)OEt], 2.93 (d, 3, $NHCH_3$), 3.30 (s, 3, hydrazide CH_3), 4.14 (q, 2, CH_2CH_3), 6.67 (d, J = 9 Hz, 1, ArH_3), 7.07 (q, 1, NH), 8.10 (d, J = 9 Hz, 1, ArH_4), 8.30 (s, 1, ArH_6).

Anal. Calcd for $C_{13}H_{18}N_4O_4$: C, 53.10; H, 6.16; N, 19.06. Found: C, 52.88; H, 6.27; N, 18.85.

The solid which remained after lixiviation was recrystallized from ethanol, affording 5.40 g (44%) of **3f** as fine yellow needles: mp 185.5–186.0 °C; ir (KBr) 1660 (shoulder C=O), 1635 (C=N), 1600 (Ar, C=C), 1520 and 1340 cm^{-1} (C–NO_2); NMR ($CDCl_3$) δ 2.18 (s, 3, C_2CH_3), 3.20 (s, 3, N_1CH_3), 3.34 (s, 3, N_4CH_3), 7.04 (d, J = 9 Hz, 1, H_9), 8.21 (d, J = 9 Hz, 1, H_8), 8.70 (s, 1, H_6).

2-Methylamino-5-nitrobenzoic Acid 2-*N*-(1-Methoxy)benzylidene-1-*N*-methylhydrazide (5). 2-Methylamino-5-nitrobenzoic acid 1-methylhydrazide (**1g,** 6.72 g, 0.030 mol) and 2-methoxyethyl ether (40 ml) were heated to reflux and treated, by dropwise addition, with 6.35 g (0.03 mol) of trimethyl orthobenzoate. After 20 h of refluxing, the solvent and other volatile products were removed in vacuo. Crystallization of the brown liquid was effected by vigorous stirring in ether followed by addition of petroleum ether. The solid which slowly precipitated was washed with ether and was dried in vacuo; 6.30 g (68%) of **5** was obtained. Recrystallizations from ethanol afforded **28** as analytically pure needles: mp 155.0–155.5 °C; ir (KBr) 3380 (N–H), 1655 (shoulder C=O), 1625 (C=N), 1580 (Ar, C=C), 1540 and 1320 cm^{-1} (C–NO_2); NMR ($CDCl_3$) δ 2.64 (d, 3, $NHCH_3$), 3.30 (s, 3, hydrazide CH_3), 3.98 (s, 3, OCH_3), 6.22 (q, 1, NH), 6.41 (d, J = 9 Hz, 1, ArH_6), 7.00–7.50 (m, 5, C_6H_5), 7.94–8.32 (m, 2, ArH_3 and $-H_4$).

Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.66; H, 5.30; N, 16.38. Found: C, 59.72; H, 5.47; N, 16.28.

Methyl 2-Ethoxymethyleneiminobenzoate (6). A mixture of 75.5 g (0.50 mol) of methyl anthranilate and 111.0 g (0.75 mol) of triethyl orthoformate was heated to reflux. The ethanol which was given off was collected in a Barrett receiver and was removed as it accumulated. Refluxing was terminated after 75 ml (58 g) of ethanol had accumulated. The excess ortho ester was evaporated in vacuo giving a dark red liquid. The product was purified by distillation under reduced pressure with the product fraction distilling at 92–97 °C under 0.1–0.03 mm. The ester (46.0 g) was obtained in 45% yield. An additional distillation afforded analytically pure ester: bp 91 °C (0.1 mm); ir (neat) 1735 (C=O), 1655 (C=N), 1185 and 1075 cm^{-1} (C–O); NMR (neat) δ 1.25 (t, 3, CH_2CH_3), 3.70 (s, 3, OCH_3), 4.24 (q, 2, CH_2CH_3), 6.60–7.45 (m, 3, ArH_3, $-H_4$, $-H_5$), 7.51 (s, 1, N=CHOEt), 7.75 (d, J = 8 Hz, 1, ArH_6).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.75; H, 6.33; N, 6.54.

Acknowledgments. The authors wish to thank Stuart Pharmaceuticals, Division of ICI United States Inc., for their generous support of this project abstracted, in part, from the Ph.D. Thesis of R.W.L. (Lehigh University, 1975). William E. Adams is acknowledged for valuable technical assistance.

Registry No.—**4,** 59169-99-2; **5,** 59170-00-2; **6,** 59204-51-2; triethyl orthoformate, 122-51-0; triethyl orthoacetate, 78-39-7; triethyl orthopropionate, 115-80-8; trimethyl orthobenzoate, 707-07-3; methyl anthranilate, 134-20-3.

References and Notes

(1) C. Podesva, G. Kohan, and K. Vagi, *Can. J. Chem.*, **47,** 489 (1969).
(2) Ferlux-Chimie S. A., French Patent 2 191 893; *Chem. Abstr.*, **81,** 25703s (1974).
(3) M. Nair, *Indian J. Chem.*, **11,** 109 (1973).
(4) A. Langis and M. Charest, *Chim. Ther.*, **2,** 349 (1967).
(5) A. Langis, U.S. Patent 3 542 767; *Chem. Abstr.*, **74,** 88089 (1971).
(6) D. Bailey, U.S. Patent 3 607 866; *Chem. Abstr.*, **75,** 140910v (1971).
(7) N. P. Peet and S. Sunder, *J. Org. Chem.*, **40,** 1909 (1975).
(8) R. W. Leiby, Jr., and N. D. Heindel, *Synth. Commun.*, submitted.
(9) T. F. Lemke, H. W. Snady, and N. D. Heindel, *J. Org. Chem.*, **37,** 2337 (1972).
(10) Another paper by S. Sunder, N. P. Peet, and D. L. Trepanier, describing compounds **2a,e,** and **l,** appears in this issue.

Preparation of New Nitrogen-Bridged Heterocycles. Reaction of Pyridinium *N*-Imines with Azirine Derivatives

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Monocyclic and bicyclic pyridinium *N*-imine salts **2–5, 10–12,** and **16–19** reacted smoothly with 2-phenylazirine (**1**) in the presence of alkali at room temperature to give the corresponding 3-phenyl-1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives **6–9, 13–15,** and **20–24** in fairly good yields, and quinolinium **26** and isoquinolinium *N*-imine dimer **27** reacted with 2,3-diphenylazirine **25** in refluxing benzene to afford 2,3-diphenyldihydropyridotriazines **28** and **29** in 90 and 93% yields, respectively. Utility of pyridinium *N*-imine as a trapping agent for transient azirine was proven in Neber reaction of acetophenone oxime *O*-tosylate **30** in the presence of pyridinium *N*-imines. Structural elucidation of these products was accomplished by physical and spectral means and by comparison with similar pyridotriazines prepared earlier by us. Possible mechanisms of this reaction are also discussed.

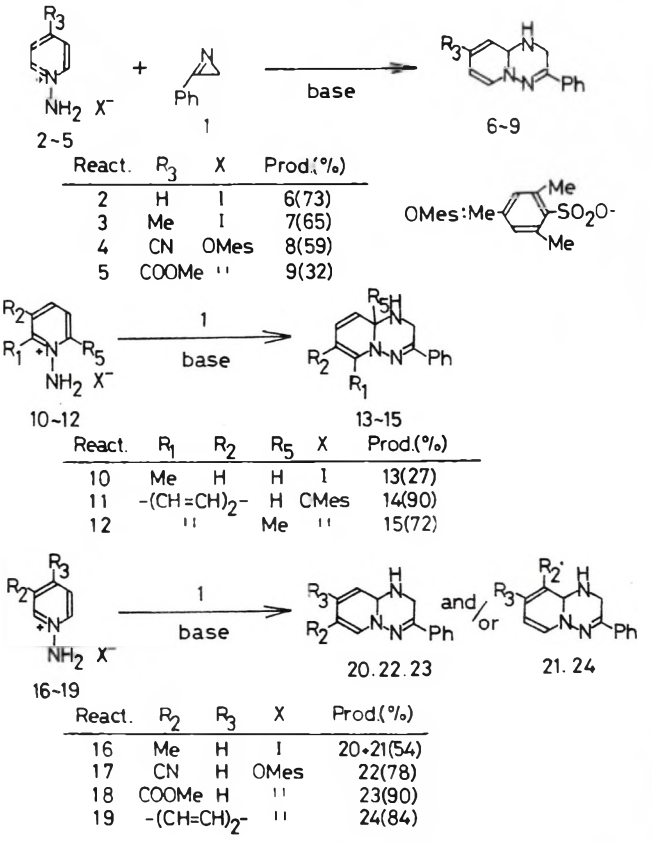
The unexpected formation of several 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives from the reactions of pyridinium *N*-imines with α-haloacrylates[1] prompted us to examine the possible intermediates involved in this reaction and to find a new synthetic route for this class of compound using such intermediates. Mechanistic consideration suggested intervention of a haloaziridine or azirine derivative, and support for the latter intermediate was obtained from the reaction of pyridinium *N*-imine with 2-phenylazirine.[2] The reaction with azirines is superior to that with α-haloacrylates for preparation of dihydropyridotriazines, since extension to a wide variety of pyridinium *N*-imines is possible and the yields are generally high. This paper describes preparation of 1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazines from the reactions of various pyridinium *N*-imines with azirines and the trapping of transient azirine using pyridinium *N*-imine.

Results and Discussion

Reactions of Pyridinium *N*-Imines with Azirine Derivatives. The reactions of pyridinium *N*-imine salts **2–5, 10–12,** and **16–19** with 2-phenylazirine **1** were carried out in methylene chloride or chloroform in the presence of potassium carbonate or basic ion-exchange resin (Amberlite IRA 410) at room temperature. These results are summarized in Scheme I.

The reactions of the parent **2** and 4-substituted pyridinium *N*-imine salts **3–5** with azirine **1** gave the corresponding adducts **6–9** in 73, 65, 59, and 32% yields, and those of 2-substituted *N*-imine salts **10–12** afforded also adducts **13–15** in 27 (crude), 90, and 72% yields, respectively. In the latter cases, decreased yields of the adduct due to steric hindrance of the 2-substituent on the pyridine ring were observed with the monocyclic *N*-imine salt **10,** but not in the bicyclic compounds **11** and **12.** Similar reactions of unsymmetrically substituted

Scheme I

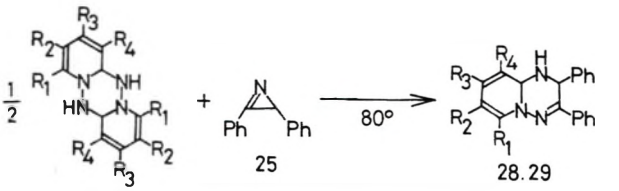


pyridinium *N*-imine salts **16–19** gave regioselectively or regiospecifically the corresponding products **20** and **21, 22, 23,** and **24** in 54 (total yield), 78, 90, and 84% yields. The ratio of

compound **20** to **21** was 1:6 (determined by NMR spectroscopy); the trend toward predominant cyclization at the more sterically hindered site on a pyridine ring has been seen frequently in cycloaddition and cyclization of 3-picolinium *N*-imine derivatives.[3-5] On the other hand, inverse orientation to sterically less hindered site was observed in the cases of *N*-imine salts **17** and **18**, bearing an electron-withdrawing group at the 3 position, with azirine **1**, in contrast to the course of the 1,3-dipolar cycloaddition of the same *N*-imine with ethyl propiolate.[4] Although 2,3-diphenylazirine **25** did not react with these pyridinium *N*-imines at room temperature, quinolinium **26** and isoquinolinium *N*-imine dimer **27** reacted smoothly with this azirine **25** in refluxing benzene to afford the crystalline products **28** and **29** in 90 and 93% yields, respectively (Scheme II). When some imidazolium and thiazolium *N*-imine salts were allowed to react with 2-phenylazirine **1** under similar reaction conditions, however, complex mixtures were formed and attempts to detect the corresponding triazine derivatives were unsuccessful.

These adducts, in particular **6–9, 13–15,** and **20–24,** were quite unstable and decomposed gradually even on storage at room temperature. Furthermore, treatment of some dihydropyridotriazines **6, 7,** and **14** with dehydrogenating agents such as palladium on carbon (5%) and tetracyanoethylene gave only tarry materials.

Scheme II



React.	R_1	R_2	R_3	R_4	Prod.(%)
26	$-(CH{=}CH)_2-$		H	H	28(90)
27	H	H	$-(CH{=}CH)_2-$		29(93)

Compounds **6–9, 13–15, 20–24, 28,** and **29** were 1:1 adducts of the corresponding pyridinium *N*-imines and 2-phenylazirine **1** or 2,3-diphenylazirine **25,** and their ir spectra showed characteristic absorptions of a secondary amino group at 3200–3270 cm^{-1} and of a carbon–carbon or carbon–nitrogen double bond at 1620–1654 cm^{-1}. The ^1H NMR spectra of these adducts (see Table I) are grossly similar to one another and also to those of dihydropyridotriazines reported earlier by us.[1] For example, the spectrum of compound **6** exhibited signals due to five protons on the dihydropyridine ring at δ ($CDCl_3$) 4.74 (1 H, br t, J = 7.5, 7.5, 1.5 Hz, C_7 H), 5.23 (1 H, br d, J = 11.0 Hz, C_9 H), 5.42 (1 H, br s, C_{9a} H), 5.99 (1 H, m,

Table I. ^1H NMR Spectral Data of Dihydropyridotriazines

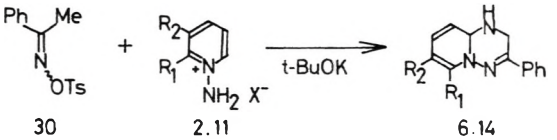
Compd	C_6	C_7	C_8	C_9	C_{9a}	NH	C_2		Ph
6	6.62 (d)	4.74 (br t)	5.99 (m)	5.23 (br d)	5.42 (br s)	2.00 (br s)	4.07 (d)	3.74 (d)	7.1–7.5 (m)
				$J_{6,7} = J_{7,8} = 7.5, J_{8,9} = 11.0, J_{6,8} = 1.5, J_{2,2} = 18.0$ Hz					
7	6.63 (d)	4.68 (dd)	1.79 (d)	5.03 (br s)	5.37 (br s)	1.96 (br s)	4.11 (d)	3.79 (d)	7.2–7.7 (m)
				$J_{6,7} = 7.5, J_{8,9} = 1.5, J_{7,9} = 1.0, J_{2,2} = 18.0$ Hz					
8	6.64 (d)	4.70 (dd)		5.68 (br s)	5.47 (br s)	2.27 (br s)	4.08 (d)	3.81 (d)	7.1–7.6 (m)
				$J_{6,7} = 7.5, J_{7,9} = 1.0, J_{2,2} = 17.5$ Hz					
9	6.67 (d)	5.22 (dd)	3.75 (s)	6.15 (br s)	5.52 (br s)	2.10 (br s)	4.13 (d)	3.82 (d)	7.1–7.6 (m)
				$J_{6,7} = 7.5, J_{7,9} = 1.0, J_{2,2} = 18.0$ Hz					
13	2.10 (s)	4.66 (br d)	5.93 (m)	5.23 (br d)	5.30 (br s)	2.00 (br s)	4.12 (d)	3.75 (d)	7.1–7.6 (m)
				$J_{7,8} = 7.5, J_{8,9} = 11.0, J_{2,2} = 18.5$ Hz					
14	6.5–7.7 (m)		6.34 (d)	5.53 (dd)	5.26 (br s)	2.02 (br s)	4.06 (d)	3.75 (d)	7.0–7.7 (m)
				$J_{8,9} = 9.5, J_{9,9a} = 2.0, J_{2,2} = 18.5$ Hz					
15	6.5–7.7 (m)		6.24 (d)	5.45 (d)	1.30 (s)	2.00 (br s)	3.91 (d)	3.63 (d)	7.0–7.7 (m)
				$J_{8,9} = 10.0, J_{2,2} = 17.5$ Hz					
20		1.71 (s)							
21	6.58 (d)	4.73 (t)	5.78 (br d)	1.83 (s)	5.30 (br s)	1.90 (br s)	4.12 (d)	3.81 (d)	7.1–7.7 (m)
				$J_{6,7} = J_{7,8} = 7.5, J_{2,2} = 18.5$ Hz					
22	7.1–7.4		6.00 (dd)	5.23 (dd)	5.45 (m)	2.02 (br s)	3.98(2H) (br s)		7.1–7.7 (m)
				$J_{8,9} = 10.0, J_{6,8} = 1.5, J_{9,9a} = 2.5$ Hz					
23	7.68 (d)	3.68 (s)	6.50 (dd)	5.21 (dd)	5.37 (br s)	1.97 (br s)	4.10 (d)	3.84 (d)	7.2–7.6 (m)
				$J_{8,9} = 10.0, J_{6,8} = 1.5, J_{9,9a} = 2.5$ Hz					
24	6.70 (d)	5.37 (d)	6.8–7.7 (m)		5.68 (s)	2.03 (br s)	4.16 (d)	3.89 (d)	7.1–7.7 (m)
				$J_{6,7} = 7.5, J_{2,2} = 17.5$ Hz					
28	6.6–7.8 (m)		6.30 (dd)	5.40 (dd)	5.28 (br s)	2.35 (br s)	4.83 (s)		7.0–7.8 (m)
				$J_{8,9} = 10.0, J_{8,9a} = 2.0, J_{9,9a} = 2.0$ Hz					
29	6.88 (d)	5.43 (d)	6.9–7.8 (m)		5.65 (br s)	2.50 (br s)	5.11 (s)		7.1–7.8 (m)
				$J_{6,7} = 7.5$ Hz					

C_8 H), and 6.62 (1 H, d, J = 7.5 Hz, C_6 H), an amino proton at δ 2.00 (1 H, br s, disappeared with deuterium oxide), two methylene protons at δ 3.74 (1 H, d, J = 18.0 Hz) and 4.07 (1 H, d, J = 18.0 Hz), and five aromatic protons at δ 7.1–7.5 (m). The chemical shifts of methylene protons at δ 3.74 and 4.07 indicated clearly that this methylene group is not involved in an aziridine ring of the primary 1,3-dipolar cycloadduct of pyridinium *N*-imine with azirine **1**, since signals due to the methylene group involved in an aziridine ring have appeared usually in a much higher region (δ 1.0–2.0).[6] Similarly, the signals of four protons on the dihydropyridine ring of compound **23** appeared at δ 5.21 (1 H, dd, J = 10.0, 2.5 Hz, C_9 H), 5.37 (1 H, br s, C_{9a} H), 6.50 (1 H, dd, J = 10.0, 1.0 Hz, C_8 H), and 7.68 (1 H, d, J = 1.0 Hz, C_6 H), and their spectral patterns and the absence of signal due to C_7 H ruled out the structure of isomeric 9-methoxycarbonyldihydropyridotriazine for this compound **23**. The value (δ 1.30) of methyl protons in compound **15** indicated that this methyl group is a substituent on sp^3 carbon[7] and hence compound **15** was realized to be an adduct cyclized at the 2 position on a quinaldine ring. From these results, we concluded that these products are 3-phenyl-**6–9, 13–15,** and **20–24** and 2,3-diphenyl-1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives **28** and **29**.

Neber Reaction of Acetophenone Oxime *O*-Tosylate 30 in the Presence of Pyridinium *N*-Imines. The intermediacy of azirine derivatives in Neber and related reactions has been well established and in some cases azirines have been actually isolated.[8–11] As a variation of the above reaction, we examined the possibility of use of azirine intermediates in the Neber reaction instead of compounds **1** and **25** employed here.

As might be expected, when acetophenone oxime *O*-tosylate **30** was treated with potassium *tert*-butoxide in tetrahydrofuran in the presence of pyridinium *N*-imine salt **2** or **11** at room temperature, the corresponding adduct **6** or **14** was formed in 50 or 65% yield (Scheme III). These products were

Scheme III



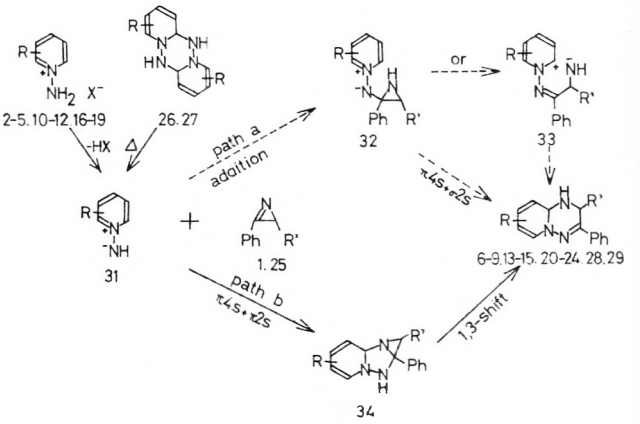
30 2.11 6.14

React.	R_1	R_2	Prod.(%)
2	H	H	6(50)
11	-(CH=CH)$_2$-		14(65)

completely in accord with dihydropyridotriazines **6** and **14** prepared above.

Mechanism. The reaction probably proceeds via initial nucleophilic addition of pyridinium *N*-imine **31** onto 2*H*-azirines **1** and **25**, followed by homo-1,5-dipolar cyclization ($_{\pi}4_s + _{\pi}2_s$) of the resulting *N*-(2-aziridinyl)iminopyridinium ylide **32** or by cyclization of 1,6-dipolar species **33** from **32** to give dihydropyridotriazines **6–9, 13–15, 20–24, 28,** and **29** (path a in Scheme IV). Similar additions of amine[12] and anionic species[13,14] on 2*H*-azirines are well known. An alternative route (path b) to pyridotriazines involves initial 1,3-dipolar cycloaddition ($_{\pi}4_s + _{\pi}2_s$) of the *N*-imines **31** with azirines **1** and **25** followed by 1,3 shift of an amino hydrogen in the primary tricyclic adduct **34**. Since cycloadditions of 2*H*-azirine with a variety of 1,3-dipoles[15–18] and thermal 1,3 migration under basic conditions[19,20] have been well documented, this route (path b) can also be considered. Path a, leading to **32**, seems more probable since 1,3-dipolar cycloadditions of 2-phenylazirine **1** with various N-substituted iminopyridinium *N*-ylides[5,21,22] and pyridinium *N*-methylides[23,24] were unsuccessful and pyridinium *N*-imines and *N*-ylides tend to

Scheme IV



react as nucleophiles rather than 1,3 dipoles.[1,5,25,26] However, attempts to prepare independently the intermediate **32**, or to obtain the pyridotriazine and its oxa analogue from the reactions of pyridinium *N*-imine with alkoxyaziridine[27] and halooxirane,[28,29] were unsuccessful.

Experimental Section

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 elemental analyzer. The NMR spectra were determined with a JEOL JNM-4H-100 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The chemical shifts are expressed in δ values. The ir spectra were taken with a Jasco DS-301 spectrophotometer.

Materials. Pyridinium *N*-imine hydriodides **2, 3, 10,** and **16** and mesitylenesulfonates **3–5, 11, 12,** and **17–19** were prepared by Gösl's[30] and Tamura's[31,32] methods, and quinolinium **26** and isoquinolinium *N*-imine dimer **27** were obtained from the reactions of the corresponding *N*-imine salts **11** and **19** with base in *N,N*-dimethylformamide.[33] Azirines **1** and **25**[34,35] and acetophenone oxime *O*-tosylate **30**[9] were also synthesized according to the literature.

Reactions of Pyridinium *N*-Imines with Azirine Derivatives. Method A. An equimolar mixture (2–4 mmol) of pyridinium *N*-imine salt and 2-phenylazirine **1** was treated with large excess of potassium carbonate (5–10 g) or basic ion-exchange resin [Amberlite IRA 410, activated with aqueous NaOH solution (10%)] in methylene chloride or chloroform at room temperature for 2–4 days, and then the reaction solution was filtered to remove insoluble substances. The filtrate was concentrated under reduced pressure and the residue was separated by column chromatography (alumina) using *n*-hexane–ether as an eluent. Recrystallization of crude product from *n*-hexane or *n*-hexane–ether gave pale yellow to yellow needles of 3-phenyl-1,9a-dihydro-2*H*-pyrido[1,2-*b*]-*as*-triazine derivatives **6–9, 14, 15,** and **20–24**, but that of adduct **13** was unsuccessful. Basic ion-exchange resin was used only in the cases of pyridinium *N*-imine *O*-mesitylenesulfonates **5** and **19** with azirine **1**. These pyridinium *N*-imines did not react with 2,3-diphenylazirine **25** under this condition.

Method B. A 1:2 molar mixture of quinolinium **26** or isoquinolinium *N*-imine dimer **27** and 2,3-diphenylazirine **25** was heated under reflux in benzene for 2 h and then the solution was concentrated under reduced pressure. Separation of the residue and recrystallization from chloroform–ether afforded the corresponding 2,3-diphenyldihydropyridotriazines **28** and **29** as pale yellow crystals.

These results and some properties of dihydropyridotriazine derivatives **6–9, 13–15, 20–24, 28,** and **29** are summarized in Table II.

Neber Reaction of Acetophenone Oxime *O*-Tosylate 30 in the Presence of Pyridinium *N*-Imines. The best result was obtained by the following procedure: a 2:1 mixture of acetophenone oxime *O*-tosylate **30** (4 mmol) and pyridinium *N*-imine salt (2 mmol) was treated with potassium *tert*-butoxide (6 mmol) in tetrahydrofuran (50 ml) at room temperature for 2 days. Similar separation from the reaction mixture afforded the corresponding dihydropyridotriazine. From *O*-tosylate **30** and pyridinium *N*-imine hydriodide **2** or quinolinium *N*-imine *O*-mesitylenesulfonate **11**, dihydropyridotriazine **6**, mp 94–97 °C, or **14**, mp 126–129 °C, was obtained in 50 or 65% yield. All physical and spectral data of these products were completely in accord with those of 3-phenyldihydropyridotriazines **6** and **14** prepared by the reactions of 2-phenylazirine **1** with the corresponding pyridinium *N*-imine salts **2** and **11** in the presence of alkali.

Table II. Results and Some Properties of Dihydropyridotriazines

Compd[a]	Reactant: N-Imine	Reactant: Azirine	Yield, %	Mp, °C	Ir (KBr), cm^{-1}: NH	Ir (KBr), cm^{-1}: C=C or C=N
6	2	1	73	95–97	3225	1637
7	3	1	65	112–115	3240	1654
8	4	1	59	127–131	3260	1622
9	5	1	32	131–135	3238	1627
13	10	1	27		3260[b]	1637[b]
14	11	1	90	126–129	3248	1636
15	12	1	72	152–154	3250	1633
20 + 21	16	1	54	[c]	3200	1642
22	17	1	78	170–172	3270	1635
23	18	1	90	134–137	3240	1632
24	19	1	84	160	3224	1624
28	26	25	90	185–188	3260	1637
29	27	25	93	161–164	3270	1620

[a] **6.** Anal. Calcd for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89. Found: C, 73.93; H, 6.22; N, 19.73. **7.** Calcd for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.57; H, 6.69; N, 18.62. **8.** Calcd for $C_{14}H_{12}N_4$: C, 71.16; H, 5.12; N, 23.72. Found: C, 70.87; H, 5.03; N, 23.81. **9.** Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.88; H, 5.45; N, 15.67. **14.** Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.03; H, 5.87; N, 15.92. **15.** Calcd for $C_{18}H_{17}N_3$: C, 78.51; H, 6.22; N, 15.26. Found: C, 78.22; H, 6.17; N, 15.41. **20 + 21.** Calcd for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.63; H, 6.75; N, 18.44. **22.** Calcd for $C_{14}H_{12}N_4$: C, 71.16; H, 5.12; N, 23.72. Found: C, 70.86; H, 5.08; N, 23.85. **23.** Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.82; H, 5.34; N, 15.56. **24.** Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.14; H, 5.83; N, 15.89. **28.** Calcd for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45. Found: C, 81.61; H, 5.83; N, 12.58. **29.** Calcd for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45. Found: C, 81.59; H, 5.58; N, 12.35. [b] Neat. [c] Mixture.

Registry No.—**1**, 7654-06-0; **2**, 6295-87-0; **3**, 7583-92-8; **4**, 39996-45-7; **5**, 59247-63-1; **6**, 54855-55-9; **7**, 54855-56-0; **8**, 59247-64-2; **9**, 59065-85-9; **10**, 7583-90-6; **11**, 39996-55-9; **12**, 39996-56-0; **13**, 59065-81-5; **14**, 59065-86-0; **15**, 59065-87-1; **16**, 7583-91-7; **17**, 39996-44-6; **18**, 56000-42-1; **19**, 39996-57-1; **20**, 59065-82-6; **21**, 59065-78-0; **22**, 59065-83-7; **23**, 59065-84-8; **24**, 59247-65-3; **25**, 16483-98-0; **26**, 7184-52-3; **27**, 31436-50-7; **28**, 59247-66-4; **29**, 59247-67-5; **30**, 26370-56-9.

References and Notes

(1) A. Kakehi and S. Ito, *J. Org. Chem.*, **39**, 1542 (1974).
(2) A. Kakehi, S. Ito, and T. Manabe, *J. Org. Chem.*, **40**, 544 (1975).
(3) Y. Tamura, N. Tsujimoto, and M. Ikeda, *Chem. Commun.*, 310 (1971).
(4) Y. Tamura, Y. Sumida, Y. Miki, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 406 (1975).
(5) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **37**, 3106 (1972).
(6) S. J. Brios, *J. Org. Chem.*, **27**, 3532 (1962).
(7) Similar chemical shifts of 3a-methyl protons in 1,3a- and 3,3a-dihydropyrazolopyridines are δ 1.1–1.5. See ref 5 and T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **36**, 2978 (1971).
(8) P. W. Neber and A. Burgard, *Justus Liebigs Ann. Chem.*, **493**, 281 (1932).
(9) P. W. Neber and G. Huh, *Justus Liebigs Ann. Chem.*, **515**, 283 (1935).
(10) P. A. S. Smith and E. E. Most, *J. Org. Chem.*, **22**, 358 (1957).
(11) D. F. Morrow, M. E. Butler, and E. C. Muang, *J. Org. Chem.*, **30**, 579 (1965).
(12) R. E. Moerck and M. A. Battiste, *J. Chem. Soc., Chem. Commun.*, 782 (1974).
(13) S. Sato, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 2936 (1967).
(14) S. Sato, *Bull. Chem. Soc. Jpn.*, **41**, 1440 (1968).
(15) V. Nair, *J. Org. Chem.*, **33**, 2121 (1968).
(16) V. Nair, *Tetrahedron Lett.*, 4831 (1971).
(17) K. Matsumoto and K. Maruyama, *Chem. Lett.*, 759 (1973).
(18) J. H. Bowie, B. Nussey, and A. D. Ward, *Aust. J. Chem.*, **26**, 2547 (1973).
(19) Pyridinium *N*-imines are also basic substances.
(20) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).
(21) K. Hafner, D. Zinser, and K. L. Moritz, *Tetrahedron Lett.*, 1733 (1964).
(22) T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron Lett.*, 5245 (1972).
(23) F. Krohnke, *Ber.*, **68**, 117 (1935).
(24) Y. Tamura, Y. Sumida, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 2091 (1973).
(25) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **36**, 2451 (1971).
(26) T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron*, **28**, 1469 (1972).
(27) H. E. Baumgarten and J. M. Petersen, *Org. Synth.*, **41**, 82 (1961).
(28) J. Villieras, G. Lavielle, and J.-C. Conbret, *Bull. Soc. Chim. Fr.*, 898 (1971).
(29) A. Takeda, S. Tsuboi, and I. Nakashima, *Bull. Chem. Soc. Jpn.*, **48**, 1067 (1975).
(30) R. Gösl and A. Meuwsen, *Org. Synth.*, **43**, 1 (1963).
(31) Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Lett.*, 4133 (1972).
(32) Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, and M. Ikeda, *J. Org. Chem.*, **38**, 1239 (1973).
(33) T. Okamoto, M. Hirobe, and T. Yamazaki, *Chem. Pharm. Bull.*, **14**, 512 (1966).
(34) A. Hassner and F. W. Fowler, *Tetrahedron Lett.*, 1545 (1967).
(35) M. Komatsu, S. Ichijima, Y. Ohshiro, and T. Agata, *J. Org. Chem.*, **38**, 4341 (1973).

Oxidation of Primary Amines and Indoline with Palladium Dichloride and Gold Trichloride

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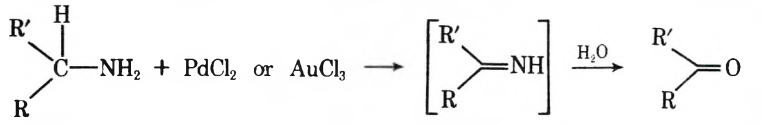
Primary amines were oxidized in water by $PdCl_2$ and $AuCl_3$ with isolated product yields of 2.5–72% depending on reaction pH and structure of the amine. The oxidation of indoline to indole gave isolated yields of 0–83% depending on reaction conditions, with the optimum reaction in methanol and triethylamine at room temperature.

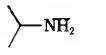
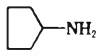
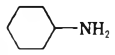
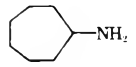
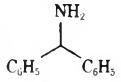
In contrast to the oxidation of alcohols with palladium dichloride, the far less universal oxidation of amines to carbonyl compounds has not been previously explored with this reagent. Alcohols are found to undergo 50–100% conversions to carbonyl compounds with palladium dichloride.[2-4] In these oxidations, yields are sometimes greater than 100%, based on the amount of palladium dichloride used, because of a catalytic dehydrogenation effect of the generated metallic palladium.[3] Oxidations of alcohols can also be achieved with catalytic amounts of palladium dichloride under 3 atm of oxygen in the presence of cupric chloride or nitrate.[4]

Oxidations of tetrahydroquinoline to quinoline in 102% yield and of tetrahydroisoquinoline to isoquinoline in 130% yields (based on $PdCl_2$) again indicate a catalytic dehydrogenation by the generated palladium metal. In a corollary study heating of primary or secondary amines over metallic palladium led to more highly N-alkylated products.[5] Successive dehydrogenation, condensation, and hydrogenation steps were postulated for these reactions. The dehydrogenation of indoline to indole at 100–150 °C over a palladium on charcoal catalyst again demonstrates this reaction.[6]

A comparison of the half-wave potential for Pd^{2+} to Pd^0 (E^0

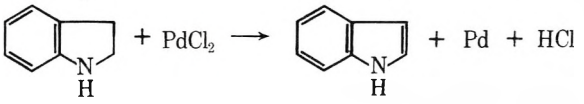
Table I. Oxidation of Primary Amines with Palladium Dichloride and Gold Trichloride



Amine[e]	Product	Isolated yield, % $PdCl_2$	Isolated yield, % $HAuCl_4$
		52[a]	23 (pH 1)[a,d] 72 (pH 5.8)[c,d]
		2.5,[a,d] 11[b,d]	9 (pH 4.5)[c,d]
		6.4[a,d]	0 (pH 1)[a] 60 (pH 5.3)[c] 50 (pH 6.8)[c]
		57[a]	52 (pH 4.5)[c] 36 (pH 6.2)[c]
		21,[a] 54[b]	20 (pH 1)[a,d] 29 (pH 6)[c,d]
		Trace[a]	48 (pH 4.5)[c]
$C_6H_5—CH_2NH_2$	$C_6H_5—CHO$	27[a]	
$C_6H_5—CH_2CH_2NH_2$	$C_6H_5—CH_2CHO$	19[a]	10 (pH 5.8)[c]
	$C_6H_5—CH_2CO_2H$		30 (pH 5.8)[c]

[a] Product of 1 equiv of oxidizing agent in water (method a). [b] Addition of 10% Pd/C catalyst to reaction mixture (method b). [c] Adjustment of initial pH with NaOH (method c). [d] Isolated as 2,4-dinitrophenylhydrazone. [e] Registry no. are, respectively, 75-31-0, 1003-03-8, 108-91-8, 5452-35-7, 98-84-0, 91-00-9, 100-46-9, 64-04-0.

Table II. Oxidation of Indoline to Indole with $PdCl_2$



Reactant	Conditions[a]	Yield, %
Indoline lithium salt[b]	THF, 0 °C	42
Indoline lithium salt	THF–TEA, r.t.	68
Indoline Pd salt (no $PdCl_2$)[c]	H_2O–NaOH, reflux	37
Indoline[d]	Methanol–TEA, r.t.	83
Indoline	TEA, r.t.	Trace
Indoline	THF, r.t.	0
Indoline	H_2O–HCl, steam dist	70
Indoline	H_2O–HCl, 10% Pd/C, r.t.	27
Indoline (no $PdCl_2$)	H_2O–HCl, 10% Pd/C, reflux	13

[a] THF = tetrahydrofuran, TEA = triethylamine. [b] Registry no., 59092-48-7. [c] Registry no., 59092-49-8. [d] Registry no., 496-15-1.

= 0.99) with those for Au^{3+} and Au^{+} to Au^0 (E^0 = 1.50 and 1.68)[7] suggests that gold salts should be even more powerful oxidizing agents for amines. However, they have apparently not been explored as reagents in organic synthesis.[8] Although the formation of metallic gold from reactions of gold trichloride with amino acids,[9] piperidine, toluidine, and naphthylamine[10] was reported and the formation[10,11] and kinetics of substitution reactions[12,13] of gold amine complexes are known, the organic products or yields of these amine oxidations were not given. Metallic gold has also been used for catalytic dehydrogenations, but it seems to be less effective than palladium in this respect.

Oxidations of the primary amines shown in Table I with $PdCl_2$ or $HAuCl_4$ were achieved by combining the amine and oxidizing agent in water and distilling the reaction mixture to dryness (method a). The steam distilled carbonyl compounds thus formed by hydrolysis of initial imine products were quantitatively characterized by isolation, dinitrophenylhydrazone formation, and gas chromatography. Since a catalytic effect of palladium metal was anticipated, 10% palladium on charcoal was added to the reaction mixture of cyclopentyl- and α-phenethylamines, with a resultant multiplication of yields (method b). It may be noted that in absence of $PdCl_2$ the palladium on charcoal did not give any oxidation of cyclopentylamine, cyclohexylamine, or β-phenethylamine but that low-yield oxidations of α-phenethylamine to acetophenone and of indoline to indole could be seen under those conditions.

It has been shown that aqueous solutions of chloroauric acid at a pH near 1 contain gold coordinated primarily as $AuCl_4^-$, at pH 4 as $AuCl_3OH^-$, at pH 5.5 as $AuCl_2(OH)_2^-$, at pH 7 as $AuCl(OH)_3^-$ with Au_2O_3 precipitating at a pH above 7.[14] Thus it was of interest to study the amine oxidations with an adjustment of the initial pH of the reaction mixtures (method c). Highest yields were invariably found in weakly acidic solutions. These results may reflect an optimum gold–amine coordination or alternatively optimum conditions for balancing amine complexation and imine product dissociation and hydrolysis.

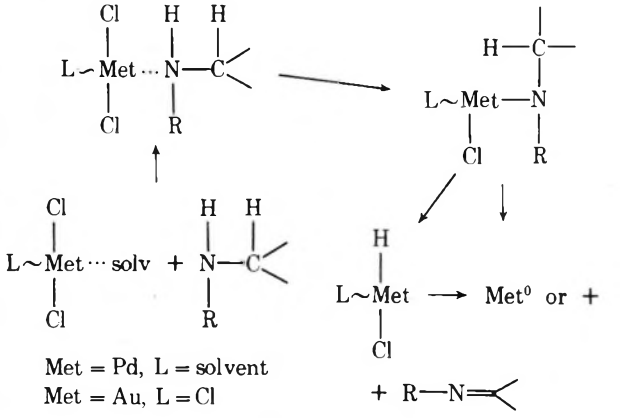
The formation of aldehydes or ketones by oxidation of

secondary amines with $PdCl_2$ or $AuCl_3$ was less successful. Thus di-*n*-butylamine gave only traces of butyraldehyde with $PdCl_2$, diethylamine produced a 7.2% yield of acetaldehyde when oxidized with $HAuCl_4$, and *N*-phenylcyclohexylamine yielded no cyclohexanone with the latter reagent at pH 6.

However, indoline was readily oxidized to indole by $PdCl_2$. Yields corresponding to various reaction conditions are shown in Table II. The most successful indoline oxidation was found to be one in which triethylamine had been added. Since indole rather than a more basic imine is formed in this reaction (in contrast to the preceeding amine oxidations) neutralization of the generated hydrochloric acid is required.

From attempted oxidations of indoline with $AuCl_3$ at pH 1 or 4, very little indole could be isolated.

As amine complexes of palladium and gold have been characterized,[11-13,15] and palladium amides are well known,[15] one may assume that the present amine oxidations proceed at least through the first, and possibly both of these intermediates, depending on pH. Subsequent imine formation may then take place either by direct generation of Pd^0 or Au^+ or through metal hydride intermediates[2,3,16] and their subsequent decomposition. The formation of metallic gold requires an additional disproportionation or amine redox reaction or the formation of larger amine complexes (3:2 amine:$AuCl_3$).



Experimental Section

General. Many of the palladium dichloride reactions reported in this section were performed by a general procedure. The palladium dichloride was dissolved in water containing a small amount of hydrochloric acid and the amine was added. The reaction mixture was then heated and distilled rapidly to dryness at atmospheric pressure. Where the expected product was a low molecular weight ketone or aldehyde, the distillate was collected in a receiving flask containing 2,4-dinitrophenylhydrazine reagent. The higher molecular weight ketones were extracted from the aqueous distillate with ether using a liquid–liquid extractor or with dichloromethane. The organic extract was then dried and condensed yielding the product which was analyzed either as the pure compound or its 2,4-DNP derivative. The following oxidations of isopropylamine and α-methylbenzylamine are representative of the general method used. Other reactions performed under similar conditions are given in abbreviated form. Reactions which were not performed by this general procedure are described fully. All of these reactions were performed under a nitrogen atmosphere.

Reaction of Isopropylamine with Palladium Dichloride. Palladium dichloride (0.3 g, 1.7 mmol) was dissolved in 25 ml of water containing enough hydrochloric acid to maintain complete solution. Freshly distilled isopropylamine (0.5 g, 8.5 mmol) was added and the solution was distilled to a paste into a receiving flask containing 15 ml of saturated 2,4-DNP reagent. The precipitate was filtered, recrystallized once from ethanol, and dried yielding a yellow hydrazone (0.21 g, 52%) which was identified as acetone 2,4-DNP by TLC and mixture melting point comparison with an authentic sample (mp 124–125 °C, lit.[15] 125–126 °C).

Reaction of α-Methylbenzylamine with Palladium Dichloride and Palladium Metal. Palladium dichloride (0.19 g, 1.07 mmol), α-methylbenzylamine (0.20 g, 1.65 mmol), and 10% palladium on carbon (0.4 g, 0.38 mg-atom) were mixed in 105 ml of water containing a few drops of hydrochloric acid and the contents were distilled to dryness. The distillation apparatus was rinsed with dichloromethane and the distillate was extracted several times with dichloromethane. The organic extracts and washings were combined, dried, and concentrated, yielding a colorless oil (0.07 g, 54%) which gave a single spot on the TLC and which was identified as acetophenone by TLC, ir (1680 cm^{-1}), and mixture melting point of the 2,4-DNP derivative with an authentic sample. A 21% yield was obtained in the absence of palladium on carbon.

Reaction of α-Methylbenzylamine with Palladium Metal. α-Methylbenzylamine (0.09 g, 0.76 mmol) was added to 7 ml of water and the mixture was adjusted to a pH of approximately 5 with 10% hydrochloric acid. To this solution was added 10% palladium on carbon (0.14 g, 0.13 mg-atom) and the mixture was heated at reflux for 28 h. The mixture was then cooled, filtered through Celite, and extracted several times with dichloromethane. The combined organic extracts were dried, filtered, and evaporated, yielding a clear oil (0.11 g, 12%) which was essentially pure by TLC and VPC. The material was identified as acetophenone as described above.

Reaction of Cyclopentylamine with Palladium Dichloride and Palladium Metal. Palladium dichloride (0.35 g, 2.0 mmol), cyclopentylamine (0.12 g, 1.4 mmol), 10% palladium on carbon (0.4 g, 0.38 mg-atom), and 20 ml of water yielded cyclopentanone which was isolated as the 2,4-dinitrophenylhydrazone. The 2,4-DNP derivative was purified by dry column chromatography on 100 g of Woelm activity grade III silica gel eluted with benzene yielding the pure compound (0.04 g, 11%), mp 142–143 °C (lit.[16] 142 °C). A 2.5% yield was obtained without palladium metal. (No cyclopentanone was formed from cyclopentylamine and 10% palladium on charcoal, refluxed at pH 4.0 for 24 h in water.)

Reaction of Cyclohexylamine with Palladium Dichloride and Palladium Metal (b). Palladium dichloride (0.44 g, 2.26 mmol), cyclohexylamine (0.24 g, 2.4 mmol), 10% palladium on carbon (0.64 g, 0.60 mg-atom), and 10 ml of water were distilled in the usual way. This yielded cyclohexanone (0.04 g, 6.4%) isolated as its 2,4-DNP derivative, mp 158–159 °C (lit.[16] 160 °C). No cyclohexanone was formed in the absence of either palladium reagent.

Reaction of Cycloheptylamine with Palladium Dichloride. Cycloheptylamine (0.20 g, 1.77 mmol) and palladium dichloride (0.29 g, 1.63 mmol) gave cycloheptanone (0.11 g, 57%) isolated as the pure compound, mp 2,4-DNP derivative 147–148 °C (lit.[17] 148 °C).

Reaction of Benzylamine with Palladium Dichloride. Palladium dichloride (0.40 g, 2.3 mmol), benzylamine (0.18 g, 1.7 mmol), and 25 ml of water gave benzaldehyde (0.05 g, 27%) isolated as the pure compound, mp 2,4-DNP derivative 239–240 °C (lit.[15] 239–240 °C).

Reaction of β-Phenylethylamine with Palladium Dichloride and Palladium Metal. Palladium dichloride (0.37 g, 2.1 mmol), β-phenylethylamine (0.27 g, 2.2 mmol), 10% palladium on carbon (0.41 g, 0.4 mg-atom), and 100 ml of water yielded phenylacetaldehyde (0.05 g, 19%) isolated as the pure compound, mp 2,4-DNP derivative 110–111 °C (lit.[17] 110 °C).

Reaction of Amines with Gold Trichloride. General. Many of the reactions of amines with gold trichloride described in this section were performed by the same general procedure. The amine and chloroauric acid were combined in water and in some cases the pH was then adjusted by addition of 10% sodium hydroxide. The mixture was then heated and distilled to dryness. For low molecular weight ketones or aldehydes the distillate was collected directly into 2,4-dinitrophenylhydrazine reagent and the yield determined from the resulting hydrazone. Higher boiling products were usually isolated in pure form. The oxidation of isopropylamine is representative of the procedure used. Those reactions which were not performed by this general method are described in greater detail. The percentage yields reported in this section are based on the amount of carbonyl compound formed according to the equation $3amine + 2AuCl_3 + 3H_2O = 3carbonyl + 2Au^0 + 6HCl + 3NH_3$

Preparation of Chloroauric Acid Trihydrate (CAT). Gold powder (1.00 g, 5.08 mg-atoms) was dissolved in 8.0 ml of aqua regia prepared from nitric acid (2.0 ml), hydrochloric acid (4.0 ml), and water (2 ml). The solution was evaporated to dryness on a steam bath and 2 ml of hydrochloric acid was added. The solution was again evaporated to dryness and a second portion of hydrochloric acid was added and evaporated. The addition of hydrochloric acid was repeated again but the evaporation was stopped before complete dryness was obtained. The yellow paste was placed in a vacuum desiccator and dried at approximately 10 mm over phosphorus pentoxide for 48 h, yielding chloroauric acid trihydrate (2.01 g, 100%).

Recovery of Gold from Reaction Mixtures. All reaction vessels and filtering apparatus were washed with aqua regia and all extracts,

filter paper, and drying reagents were added. The solution was evaporated to dryness and water was added. The solution was filtered and the pH was adjusted to approximately 2 with sodium hydroxide. A saturated sodium nitrite solution (40 ml) was added in several portions and the solution was heated to boiling. The pH was then adjusted to approximately 8 with sodium hydroxide and the mixture cooled and filtered. The material which collected on the filter was washed with 10% hydrochloric acid until the wash water was colorless and then rinsed with ethanol and ether. The gold remaining accounted for approximately 86% of the gold used. This gold was used without further treatment in the formation of new gold chloride reagent.

Reaction of Isopropylamine with Gold Trichloride. A. Chloroauric acid trihydrate (0.20 g, 0.51 mmol) and isopropylamine (0.07 g, 1.2 mmol) were dissolved in 20 ml of water and the pH was adjusted to 5.8 with 10% sodium hydroxide. The mixture was then distilled to dryness under a nitrogen atmosphere and the distillate was collected in a receiving flask containing 2,4-DNP reagent. The yellow precipitate was filtered and dried yielding acetone-2,4-dinitrophenylhydrazone (0.13 g, 72%), mp 124–125 °C.

B. CAT (0.19 g, 0.48 mmol) and isopropylamine (0.10 g, 1.7 mmol) were dissolved in 20 ml of water and distilled into 2,4-DNP reagent yielding acetone 2,4-dinitrophenylhydrazone (0.04 g, 23%).

Reaction of Cyclopentylamine with Gold Trichloride. CAT (0.168 g, 0.42 mmol) and cyclopentylamine (0.12 g, 1.4 mmol) were combined in 20 ml of water at a pH of 4.3–4.5 and distilled into 2,4-DNP reagent yielding the hydrazone of cyclopentanone (0.015 g, 9%), mp 139–141 °C.

Reaction of Cyclohexylamine with Gold Trichloride. A. CAT (0.21 g, 0.53 mmol) and cyclohexylamine (0.08 g, 0.81 mmol) in 25 ml of water at a pH of 5.3 yielded pure cyclohexanone (0.45 g, 60%) after 24 h continuous extraction of the distillate with ether.

B. A 50% yield was obtained at pH 6.8.

C. CAT (0.30 g, 0.76 mmol) and cyclohexylamine (0.99 g, 0.91 mmol) in 25 ml of water at a pH of 0.9–1.1 gave no product which formed a precipitate with 2,4-DNP reagent or which corresponded to cyclohexanone by TLC.

Reaction of Cycloheptylamine with Gold Trichloride. A. CAT (0.338 g, 0.85 mmol) and cycloheptylamine (0.09 g, 0.8 mmol) in 30 ml of water at a pH of 6.0–6.2 yielded a colorless oil (0.083 g) which was distilled at 90–110 °C (8–10 mm) to give cycloheptanone (0.032 g, 36%).

B. CAT (0.133 g, 0.34 mmol) and cycloheptylamine (0.16 g, 1.4 mmol) in 20 ml of water at a pH of 4.5 yielded cycloheptanone (0.03 g, 52%).

Reaction of α-Methylbenzylamine with Gold Trichloride. A. CAT (0.30 g, 0.77 mmol) and α-methylbenzylamine (0.16 g, 1.3 mmol) in 25 ml of water were distilled into 2,4-DNP reagent to yield the 2,4-DNP derivative of acetophenone (0.069 g, 20%).

B. CAT (0.28 g, 0.71 mmol), α-methylbenzylamine (0.10 g, 0.83 mmol), and sodium carbonate (0.1 g, 0.94 mmol) in 22 ml of acetonitrile gave after 1 h a complex mixture of products. At least seven new volatile components were observed by VPC. One of these appeared to be acetophenone by retention time on TLC and VPC when compared with an authentic sample. Saturated sodium chloride solution (10 ml) was added to this solution and the mixture was extracted with benzene. The benzene extracts were dried and evaporated yielding a brown residue. This residue was treated with 2,4-DNP reagent and filtered yielding after one further recrystallization the hydrazone of acetophenone (0.017 g, 7%).

C. CAT (0.19 g, 0.48 mmol) and α-methylbenzylamine (0.13 g, 1.1 mmol) in 20 ml of water at a pH of 6.0 gave acetophenone (0.062 g, 29%) isolated as the 2,4-DNP derivative.

Reaction of Diethylamine with Gold Trichloride. CAT (0.19 g, 0.48 mmol) and diethylamine (0.07 g, 0.96 mmol) in 25 ml of water were distilled into 2,4-DNP reagent yielding a yellow solid which was recrystallized to give the hydrazone of acetaldehyde (0.014 g, 7.2%).

Reaction of β-Phenylethylamine with Gold Trichloride. CAT (0.32 g, 0.81 mmol) and β-phenylethylamine (0.10 g, 0.83 mmol) in 20 ml of water at a pH of 5.8 gave a mixture of phenylacetaldehyde and phenylacetic acid which were identified by TLC and VPC comparison with authentic samples. The colorless oil (0.04 g, ca. 40%) appeared by VPC and by the relative intensities of the carbonyl peaks in the ir spectrum to be approximately 25% aldehyde and 75% acid.

Reaction of Benzhydrolamine with Gold Trichloride. CAT (0.13 g, 0.35 mmol), benzhydrolamine (0.10 g, 0.55 mmol), and 6 ml of tetrahydrofuran were combined with 2 ml of water at a pH of 4.5–5.0 and stirred for 12 h. Ether (20 ml) was added and the solution was washed with 2 ml of 10% sodium hydroxide followed by two 2-ml portions of 5% hydrochloric acid. The organic layer was dried over magnesium sulfate, filtered, and concentrated to a colorless residue (0.080 g). TLC analysis on silica gel eluted with benzene indicated two products at R_f values of 0.41 and 0.55, respectively, and a third spot which did not move from the origin. This material was chromatographed on Woelm neutral alumina activity grade I eluted with benzene. Separation was not adequate to isolate pure compounds directly from the column. The second fraction contained a colorless oil which corresponded to the material at R_f value of 0.41 and was identified as benzophenone after recrystallization from ethanol by ir and mixture melting point comparison with an authentic sample. The first fraction contained the material with R_f 0.55 as well as some benzophenone. This material was distilled at 100–140 °C (0.001 mm) and recrystallized from benzene–ethanol yielding white crystals which were identified as benzophenonylidene benzhydrolamine, mp 153–154 °C,[18] by mixture melting melting point, ir, and mass spectra comparison with an authentic sample.

The yields of benzophenone and benzophenylidene benzhydrolamine in the total reaction mixture were determined by quantitative thin layer chromatography.[19] Thus, the reaction products (0.080 g) contained benzophenone (0.021 g, 25%) and benzophenonylidene benzhydrolamine (0.023 g, 15%). These values are the average of several experiments and are reproducible to within 5%. The total yield of benzophenone both isolated and as the Schiff base derivative was 0.033 g (48% based on gold trichloride).

Reaction of Indoline with Palladium Dichloride. A. As Lithium Salt. Indoline (0.12 g, 1.0 mmol) was treated in an addition funnel with n-butyllithium (0.5 ml, 1.0 mmol) in 2 ml of tetrahydrofuran. This solution was added slowly, under nitrogen, to a stirred solution of palladium dichloride (0.18 g, 1.0 mmol) in 2 ml of tetrahydrofuran which was cooled to 0 °C. A black precipitate formed immediately and after 10 min the reaction mixture was filtered through Celite, washed with 5% hydrochloric acid, and concentrated. The residue was chromatographed on a 30 × 1.5 cm silica gel column and eluted with 20% ether in benzene. After removal of 100 ml of solvent the next 200 ml contained indole (0.05 g, 42%).

B. With Triethylamine. Addition of 1 ml of triethylamine to this reaction mixture and stirring for 2 h at room temperature gave 0.08 g (68% yield).

C. Isolation of Pd Salt. Indoline (0.39 g, 3.2 mmol) and palladium dichloride (0.29 g, 1.61 mmol) were combined in 25 ml of chloroform. The solution was heated to reflux for 3 h and distilled to dryness at reduced pressure leaving a yellow-orange solid. This solid was treated with 25 ml of water and 5 ml of 10% sodium hydroxide under reflux for 5 min. The mixture was neutralized with hydrochloric acid, extracted with dichloromethane, and chromatographed on a 40 × 2.5 cm dry column of Woelm activity grade III silica gel eluted with ether. The indole portion was removed and extracted with ethanol, yielding indole (0.07 g, 37%).

D. In Methanol–Triethylamine. indoline (0.12 g, 1.0 mmol), palladium dichloride (0.18 g, 1.0 mmol), and triethylamine (0.1 g, 1.0 mmol) were dissolved in 3 ml of methanol and allowed to stir under nitrogen for 2 h during which time a black precipitate of palladium metal formed. The mixture was filtered through Celite, 5 ml of 10% hydrochloric acid was added, and the solution was saturated with sodium chloride and extracted with benzene. The benzene extracts were dried and evaporated yielding indole (0.10 g, 83%).

An analogous reaction mixture without triethylamine in tetrahydrofuran showed no indole after 3 days at room temperature and precipitation of Pd metal. A reaction in triethylamine for 24 hr at room temperature gave traces of indole identified by TLC and other unidentified products.

E. In Water. Indoline (0.29 g, 2.4 mmol) was added to 20 ml of water and enough 10% hydrochloric acid was added to make the solution homogeneous. Palladium dichloride (0.21 g, 1.2 mmol) was added and the reaction vessel was equipped with a short path distillation column. The flask was then heated and the reaction mixture distilled to dryness under a nitrogen atmosphere. Indole azeotroped with water and crystallized in the distillate. The distillate was neutralized with sodium carbonate and extracted with dichloromethane. The extracts were dried and evaporated yielding indole (0.10 g, 70%).

F. Palladium on Carbon Added. Indoline (0.34 g, 2.8 mmol), palladium dichloride (0.26 g, 1.47 mmol), and 10% palladium on carbon (0.10 g, 0.1 mg-atom) were combined in 30 ml of water to which enough hydrochloric acid had been added to dissolve the amine. The reaction mixture was allowed to stir for 16 h, filtered, and extracted with dichloromethane. The organic extracts were evaporated and the residue was chromatographed by preparative TLC on a Mallinckrodt ChromAR 1000 sheet eluted with benzene. The indole-containing portion was removed, extracted with ethanol, and concentrated to yield indole (0.05 g, 27%).

G. Reaction with Palladium on Carbon. Indoline (0.18 g, 1.5 mmol) was dissolved in 3 ml of water containing hydrochloric acid and the pH was adjusted to approximately 2. Palladium on carbon (0.3 g, 0.3 mg-atom) was added and the mixture was refluxed under nitrogen for 24 h. The mixture was then filtered, extracted with benzene, and treated with picric acid yielding indole picrate, 0.07 g (12% yield).

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Registry No.—Diethylamine, 109-89-7; triethylamine, 121-44-8; palladium dichloride, 7647-10-1; gold trichloride, 13453-07-1.

References and Notes

(1) Abstracted from part of Ph.D. Thesis of T. C. Hall, University of Vermont, 1974.
(2) P. M. Maitlis, Ed., "The Organic Chemistry of Palladium," Vol. II, Academic Press, New York, N.Y., 1971.
(3) A. V. Nikiforova, I. I. Moiseev, and Ya. K. Syrkin, *Zh. Obshch. Khim.*, **33**, 3239 (1963).
(4) W. G. Lloyd, *J. Org. Chem.*, **32**, 2816 (1967).
(5) G. W. Cooke and J. M. Gollard, *J. Chem. Soc.*, 872 (1939).
(6) J. M. Bakke, French Patent 1 576 807 (1969); *Chem. Abstr.*, **72**, 121360n (1970).
(7) Half-wave potentials taken from "Chemistry," D. H. Busch, H. Shull, and R. T. Conely, Ed., Allyn and Bacon, Boston, Mass., 1973, pp 446–448.
(8) While an initial cost may seem a deterrent, this reagent is relatively inexpensive compared to advanced intermediates in a multistep synthesis because of the facile recovery of metallic gold from all oxidation reactions and its simple conversion back to chloroauric acid (Au^{3+}) in aqua regia.
(9) J. K. Bowden, J. B. Weiss, and J. C. Taylor, *Electron Microsc., Proc. Eur. Congr., 5th*, 280 (1972); *Chem. Abstr.*, **79**, 75569g (1973).
(10) L. Cattalini and M. L. Tobe, *Coord. Chem. Rev.*, **1**, 106 (1966).
(11) W. H. Baddley and F. Basolo, *Inorg. Chem.*, **3**, 1087 (1964).
(12) W. J. Louw and W. Robb, *Inorg. Chim. Acta.*, **3**, 29, 303 (1969).
(13) B. I. Peshchevitskii and G. I. Shamouskaya, *Zh. Neorg. Khim.*, **17**, 2648 (1972); *Chem. Abstr.*, **78**, 8335u (1973).
(14) D. W. Gibson, M. Beer, and R. J. Barrnet, *Biochemistry*, **10**, 3669 (1971).
(15) G. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953).
(16) C. F. H. Allen, *J. Am. Chem. Soc.*, **52**, 2955 (1930).
(17) O. L. Brady, *J. Chem. Soc.*, 756 (1931).
(18) G. Charles, *Bull. Soc. Chim. Fr.*, 1576 (1963).
(19) J. P. Dixon, Ed., "Modern Methods in Organic Microanalysis," Van Nostrand, Princeton, N.J., 1968, pp 238–251, and references cited therein.

London Force and Related Coulombic Interactions in the Displacement Reaction with Substituted Benzyl Chlorides

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The reaction rate constants for the displacement reactions with ortho- and para-substituted benzyl chlorides (CH_3, Cl, Br, and I) and the nucleophiles, MeO^-, PhS^-, and I^-, are presented. After accounting for the electrical effects of the substituents, all the trends in the values of the k_o:k_p rate ratios are best explained by considering two opposing factors operating in the transition state structure, steric effects, and London and related coulombic interactions between the nucleophiles and the ortho substituents.

London forces and related coulombic interactions have long been recognized as factors affecting equilibria and reaction rates.[1] Bunnett,[2] in a theoretical paper, suggested the operation of London forces in several bimolecular nucleophilic reaction series. He attributed the enhancement of reaction rate to London forces when the transition state structure is such as to bring highly polarizable groups close to one another. Bunnett and Reinheimer[3] estimated these forces in the reaction of the o-bromo- and *o*-methylbenzyl chlorides with the nucleophiles, MeO^-, PhS^-, and I^-. Sisti,[4] simultaneously with Reinheimer,[5] offered a new method of comparing the rates from that of Bunnett.[3] Reinheimer[5] examined the *o*-CH_3:*p*-CH_3 and o-Br:*p*-Br reaction rate ratios of benzyl chlorides with the same nucleophiles and obtained a better correlation of theory and experimental results than Bunnett.[3] He demonstrated that calculations of the magnitude of London forces operating in the transition state indicated that the differences in the rate ratios with MeO^-, PhS^-, and I^- for a given substituent may be assigned to these forces. However, it was pointed out by Sisti[4] that comparison of the *o*-CH_3:*p*-CH_3 and o-Br:*p*-Br rate ratios with any given nucleophile did not show the trends expected from London interactions alone, i.e., charged nucleophiles invariably gave higher ortho:para rate ratios with the less polarizable methyl group than with the more polarizable bromo group.

This paper reports the results of studies of the reaction of the nucleophiles MeO^-, PhS^-, and I^- with other ortho- and para-substituted benzyl chlorides. The purpose of the study was to determine if the trends still persist in the rate ratios and to discuss their possible origins.

Results

The reaction rate constants for the nucleophilic displacement of chloride from the ortho- and para-substituted benzyl chlorides are presented in Table I. Comparison of the results with the literature shows moderate to good agreement. Some comparisons are presented in Table I. We have confidence in our results since VPC analysis of the benzyl chlorides indicated that they were at least 99%pure. Also, the reaction rates of the nucleophiles with benzyl chloride were measured and only when found to be in acceptable agreement with the literature values were the analytical methods applied to the kinetic determinations for the substituted benzyl chlorides. The observed rate constants for the lithium methoxide runs are composites of the methoxide and solvolysis reactions. Thus, the rate constants presented in Table I are those which have been corrected for solvolysis by the method of Bunnett.[3]

Discussion

It will first be demonstrated that the trends in the k_o:k_p values (Table II) for a given ortho substituent with different nucleophiles and for any given nucleophile with different ortho substituents cannot be explained from consideration of the polar and steric effects of the substituents. A new consideration will be suggested which can, together with steric effects, satisfactorily explain the trends in the k_o:k_p values.

The polar effect for a substituent will be identical from the para and ortho positions and will cancel in the ratio, k_o:k_p, if the susceptibility constants, ρ and ρ^*, are identical. The equivalence of ρ and ρ^* has been observed to be generally true.[6] Also, the equivalence of σ_p and σ^*, a property confirmed

Table I. Rate Constants for Reactions of Substituted Benzyl Chlorides at 20 °C ($k_2 \times 10^5$ l./mol s)

Nucleophile/solvent		Substituents			
		CH_3	Cl	Br	I
LiOMe/MeOH	*p*-	2.70[a]	1.74	1.66[b]	1.60
	o-	3.58[c]	1.41[d]	1.37[c]	1.35[d]
LiSPh/MeOH	*p*-	2930[e]	3300	3500[f]	3460
	o-	7120[c]	3960[d]	3860[c]	4650[d]
NaI/Me_2CO[g]	*p*-	40.2[h]	78.0[i]	85.7[j]	81.7[k]
	o-	321[c]	146[d,l]	156[c,l]	153[d,l]
MeOH[m]	*p*-	6.53[n]	1.85	2.88[o]	3.01
	o-	15.6[p]	1.17	1.21[q]	1.36

[a] Average of two runs; extrapolated value from data in ref 5, 2.63×10^{-5}. [b] Extrapolated value from data in ref 5, 1.54×10^{-5}. [c] Value obtained by extrapolation from data in ref 3. [d] Value obtained by extrapolation to 20 °C from unpublished results of J. F. Bunnett, W. Greizerstein, D. J. McLennan, and A. A. Shiragian. [e] Average of two values; extrapolated value of 2770×10^{-5} from data in ref 5. [f] Average of two runs; extrapolated value of 3390×10^{-5} from data in ref 5. [g] For the reactions with NaI the rate constants were also (see Experimental Section) obtained from the slopes of the plots of $1/[I^-]$ vs. time. Linear plots to about 40% reaction were obtained. Beyond approximately 40% reaction the observed rates generally decreased until equilibrium was attained. All rate constants with iodide, therefore, were determined from the data obtained between 5 and 40% reaction. The concentrations of NaI employed were between 0.03 and 0.05 M.[3,5,20,d] [h] Average of two runs; extrapolated value of 38.4×10^{-5} with NaI in acetone from data in ref 5. [i] A value of 77.7×10^{-5} with KI in acetone at 20 °C from ref 20. [j] A value of 86.6×10^{-5} with KI in acetone at 20 °C from reference in *i*. [k] A value of 82.8×10^{-5} with KI in acetone at 20 °C obtained from reference in *i*. [l] Value was in good agreement with the one obtained in KI in acetone at 20 °C by reference in *i*. [m] *k*, in $s^{-1} \times 10^8$. [n] A value of 6.54×10^{-8} obtained by extrapolation of data in ref 5. [o] An extrapolated value of 2.94×10^{-8} from ref 5. [p] An extrapolated value of 15.9×10^{-8} from ref 3. [q] An extrapolated value of 1.23×10^{-8} from ref 3.

Table II. Reaction Rate Ratios for Substituted Benzyl Chlorides at 20 °C

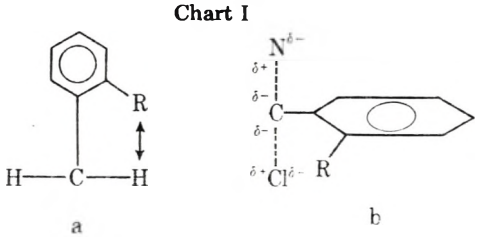
Nucleophile (N)	Solvent	$k_o:k_p$			
		CH_3	Cl	Br	I
MeO^-	MeOH	1.33[a]	0.81	0.83[b]	0.84
PhS^-	MeOH	2.43[c]	1.20	1.10[d]	1.35
I^-	Me_2CO	8.00[e]	1.87[f]	1.82[f]	1.87[f]

[a] A value of 1.43 obtained by ref 5. [b] A value of 0.84 obtained by ref 5. [c] A value of 2.61 obtained by ref 5. [d] A value of 1.18 obtained by ref 5. [e] A value of 8.16 obtained by ref 5. [f] Values for the $k_o:k_p$ rate ratios for the substituents Cl, Br, and I with KI in acetone at 20 °C obtained from data in ref 20 were 1.88, 1.69, and 1.85, respectively.

by Taft,[6] offers further support that the $k_o:k_p$ rate ratio should cancel the total polar effect. Table II, composed from the kinetic data in Table I, presents the $k_o:k_p$ ratios for the substituents with each of the nucleophiles employed.

It must also be shown that the trends in the $k_o:k_p$ rate ratios cannot be explained by the steric consideration between the ortho substituent and the nearest benzyl hydrogen (Chart I).

Chart I



R = CH_3, Cl, Br, and I; N = MeO^-, PhS^-, and I^-

Examination of the $k_o:k_p$ rate ratios for different substituents with any given nucleophile reveals that the steric effect cannot be solely responsible for their trends. It is observed (Table II) that with any given nucleophile the $k_o:k_p$ values for the methyl group are higher than the values for the bromo group of equal size[3] and higher than the values for the smaller chloro group. The trends in the $k_o:k_p$ values for the Cl, Br, and I groups with any given nucleophile are not to be expected from consideration of their steric effects alone. Also note that most $k_o:k_p$ rate ratios are >1 and increase from MeO^- to I^- for a given ortho substituent. These values and trends are also not to be expected from the steric consideration alone.[5] Solvent effects would obviously cancel in the $k_o:k_p$ ratios for a given substituent with different nucleophiles if all the data were available in the same solvent. Since this is not the case, one must consider what changes would occur in the value of the ratio $(k_o:k_p)_{I^-}$ with a change in solvent (acetone to methanol). The changes in reaction rate which accompany a change in the dielectric constant of the solvent would be incorporated in the numerator and denominator of the preceding ratio and thus its value should remain essentially unchanged.[7]

A suggested explanation for the trends in the $k_o:k_p$ rate ratios for a given ortho substituent with different nucleophiles and for different ortho substituents with a given nucleophile is that favorable London and related coulombic interactions between the nucleophile and the ortho substituent (and between ortho substituent and leaving chloride) are offsetting the steric effect in varying amounts.[8]

The polarizabilities of the nucleophiles (α_N) are suggested by the values for the ions, H–O^- 1.89, H–S^- 5.28, and I^- 7.10 (all units $cm^3 \times 10^{-24}$); the polarizabilities of the ortho substituents ($\alpha_{o\text{-sub}}$) are CH_3 2.19, Cl 2.28, Br 3.34, O–R 0.64, and I 5.11.[9] The model for the transition state structure is one in which the entering and departing groups are on a line perpendicular to the plane of the benzene ring (Chart I). Pearson's[10] discussion of polarizability leads to a reasonable inference that a dipole should exist between N and C and Cl and C in the transition state structure (Chart Ib). The essence of the discussion[10] was that a nucleophile of high polarizability can more effectively polarize its bonding electrons in the direction from N → C, thereby permitting better electrostatic interaction with a minimum of electrostatic repulsion between the remaining electrons on N and the covalent electrons on C. Thus, the more polarizable nucleophile, N, will have the larger dipole moment, μ ($\mu = qr$, q is the charge and r the distance between the charges) in the transition state structure since r will be larger (Chart Ib).

When considering the trends in the $k_o:k_p$ rate ratios for a given ortho substituent the steric effect between the given ortho substituent and the benzyl hydrogen (Chart I) should be the same for each of the nucleophiles. Three coulombic forces operating in the transition state can account for the trends in the $k_o:k_p$ values increasing toward the more polarizable nucleophile with a given ortho substituent (Table II).

The coulombic interaction, dipole$_N$–induced dipole$_{o\text{-sub}}$ ($F \propto \mu_N{}^2\alpha_{o\text{-sub}}/r^7$), between the nucleophile and ortho substituent should be favorable and become larger as the α_N increases since the more polarizable nucleophile should have the larger μ (see above and Chart Ib). The London interaction, induced dipole$_{o\text{-sub}}$–induced dipole$_N$ ($F \propto \alpha_N\alpha_{o\text{-sub}}/r^7$), between the nucleophile and ortho substituent should be favorable and increase as the α_N becomes larger. Lastly, the ion$_N$–induced dipole$_{o\text{-sub}}$ ($F \propto q_N\alpha_{o\text{-sub}}/r^5$) should be favorable but it is assumed that this force is the same for each of the nucleophiles.[11,12]

The trends in the k_o:k_p values (Table II) for a given nucleophile with the different halo substituents can be explained by considering two opposing factors present in the transition state, namely, the steric effect (*o*-halo group and benzyl hydrogen), and the London and related coulombic forces. Specifically, the increase in the steric interactions (Cl to I) is compensated for, in varying amounts, by an increase in the coulombic forces (London, dipole$_N$–induced dipole$_{o\text{-sub}}$, and ion$_N$–induced dipole$_{o\text{-sub}}$) caused by the increase in the $\alpha_{o\text{-halo group}}$ from Cl to I.[13]

Further examination of the k_o:k_p rate ratios for any given nucleophile with different ortho substituents shows that the values for the less polarizable methyl group are invariably higher relative to the more polarizable halogens. Contrary trends would have been expected from consideration of coulombic interactions together with the varying steric effect of the methyl and halo groups since the methyl group is less polarizable and larger than the chloro group and is less polarizable and equal in size to the bromo group.[3] Indeed, one would have expected the k_o:k_p values to be higher for the halogens relative to the methyl group[14] (with the possible exception of the larger and more polarizable iodo group). Three additional coulombic forces are deemed responsible for the higher values for the methyl group because of the favorable dispositions of the o-methyl group dipole ($\dashrightarrow CH_3$) with the dipole and with the charge of the nucleophile. These favorable dispositions do not occur with the dipole of the *o*-halo group ($\dashrightarrow$ X) (Chart Ib). The specific forces involved are believed to be dipole$_N$–dipole$_{\dashrightarrow o\text{-}CH_3}$ ($F \propto \mu^2{}_N\mu^2{}_{\dashrightarrow o\text{-}CH_3}/r^7$) which should also increase from MeO^- to I^- since μ_N should become larger with an increase in α_N; dipole$_{\dashrightarrow o\text{-}CH_3}$–induced dipole$_N$ ($F \propto \mu^2{}_{\dashrightarrow o\text{-}CH_3}\alpha_N/r^7$) which should also increase as the α_N increase from MeO^- to I^-; and the important intermediate range force, ion$_N$–dipole$_{\dashrightarrow o\text{-}CH_3}$ ($F \propto q_N\mu^2{}_{\dashrightarrow o\text{-}CH_3}/r^5$), which is presumed to be the same for each nucleophile.[12,15,16]

In summary, all the trends in the k_o:k_p rate ratios seem best explained by invoking the steric consideration together with offsetting London and related coulombic interactions between the nucleophile and the ortho substituent. These coulombic interactions vary in magnitude with α_N and $\alpha_{o\text{-sub}}$. Three additional forces are involved when the dispositions of the dipole$_{o\text{-sub}}$ with the dipole and with the charge of the nucleophile[16] are favorable. Specifically, the London, dipole$_N$–induced dipole$_{o\text{-sub}}$, and ion$_N$–induced dipole$_{o\text{-sub}}$[12] coulombic interactions increase with a given ortho substituent as the α_N increases, and they also increase with any given nucleophile as the $\alpha_{o\text{-sub}}$ increases. Three additional interactions, dipole$_N$–dipole$_{o\text{-}CH_3}$, dipole$_{o\text{-}CH_3}$–induced dipole$_N$, and ion$_N$–dipole$_{o\text{-}CH_3}$ favoring the methyl group, are deemed responsible for the higher k_o:k_p values for the less polarizable methyl group relative to the more polarizable halogens.[17] All of the coulombic forces discussed can be visualized from the model of the transition state structure (Chart Ib) which assumes the presence of a dipole between N and C and C and Cl.

Experimental Section[18]

Preparation and Purification of Materials. The *p*-chloro-, *p*-bromo-, and *p*-methylbenzyl chlorides were commercially available and were purified by fractionation[18] or by repeated recrystallizations: *p*-chlorobenzyl chloride, bp 59 °C (0.6 mm) (lit.[19] bp 222 °C), mp 28.5–29 °C (lit.[20] mp 29 °C); *p*-bromobenzyl chloride was recrystallized from petroleum ether, mp 38 °C (lit.[5] mp 38–39 °C); *p*-methylbenzyl chloride, bp 42 °C (0.5 mm) [lit.[5] bp 68.5–69 °C (6 mm)].

p-Iodobenzyl chloride was prepared as follows: *p*-iodotoluene was brominated according to the procedure of Goerner and Nanetz.[21] The crude benzyl bromide was then hydrolyzed with 50% aqueous acetone by refluxing for 60 h. The *p*-iodobenzyl alcohol obtained upon cooling was recrystallized (three times) from petroleum ether, mp 72 °C (lit.[20] mp 71–72 °C). The alcohol was then converted to the *p*-iodobenzyl chloride according to the procedure of Newman.[22] The chloride was recrystallized (two times) from petroleum ether, mp 53 °C (lit.[20] mp 53 °C).

Acetone, reagent grade, was treated with potassium permanganate under reflux (3 h), filtered, and distilled from anhydrous calcium oxide. Methanol, reagent grade, was distilled from sodium methoxide. The sodium iodide, reagent grade, was dried at 110 °C for 1 h prior to use. Lithium methoxide solutions were prepared by dissolving clean lithium metal in purified methanol and they were standardized against potassium hydrogen phthalate to a phenolphthalein end point. Lithium thiophenoxide solutions were prepared by dissolving thiophenol [reagent grade, bp 168–169 °C (lit.[23] bp 169 °C)] in standard solutions of lithium methoxide. In all the thiophenoxide runs a slight excess (10%) of free thiophenol was maintained. The silver nitrate and mercuric nitrate solutions were standardized against weighed amounts of sodium chloride. The bromophenol blue–diphenylcarbazone indicator was prepared by the method of Swain and Langsdorf.[24]

Evaluation of Rate Constants. With Lithium Methoxide. Runs at 20 °C were carried out in a glass-stoppered volumetric flask in a water bath regulated to ±0.05 °C. Initial concentrations of methoxide and substrate in methanol were equal in all cases at 0.050 M. The benzyl chloride was weighed into a 25-ml volumetric flask and dissolved in methanol up to the mark. The lithium methoxide solution was prepared and standardized as already mentioned. The concentrations of the nucleophile and substrate solutions were such that when 10 ml of organic chloride (1.00 M) and 50 ml of methoxide ion (0.200 M) solutions were pipetted into a 250-ml volumetric flask containing 140 ml of methanol it gave an overall concentration of 0.050 M in nucleophile and substrate. Ten-milliliter aliquots were taken (at different time intervals) and released into a 250-ml separatory funnel containing 80 ml of water, 5 ml of 0.2 N nitric acid, and 100 ml of ether. The aqueous layer was separated and titrated for chloride ion content using mercuric nitrate and 5 drops of bromophenol blue–diphenylcarbazone indicator as described by Swain.[24]

Individual apparent second-order rate constants (k_{app}) were calculated by substitution of the data obtained at each time interval into the second-order rate equation. The average k_{app} was obtained from a minimum of 12 individual k_{app} values calculated for each substrate, with no one k_{app} value deviating from another by more than 2%. All reactions were followed to 60–80% of the half-lives. The solvolytic rate constants (k_1) were determined at 20 °C by the same procedure described above. The solvolytic reactions were followed to 35–50% of the half-lives.

Rate constants observed (k_{app}) for the lithium methoxide runs are composites of the methoxide and solvolysis reactions. To correct the observed rate constants (k_{app}) for solvolysis the quantity $k_1/[RCl]_0$ is substracted from each according to Bunnett.[3] The k_2 values so obtained are given in Table I.

With Lithium Thiophenoxide. Initial concentrations of all benzyl chlorides and of lithium thiophenoxide were 0.050 M, and there was free thiophenol in excess (10%) (under N_2). Ten-milliliter samples were taken out by means of a fast delivery syringe and quenched by discharging into a 250-ml separatory funnel containing 20 ml of 0.1 N nitric acid, 80 ml of water, and 100 ml of ether. The ether layer was rinsed with water and the rinse water was combined with the aqueous layer. Five drops of concentrated nitric acid was then added, followed by the addition of 5 ml of 30% hydrogen peroxide. The next day the chloride ion content was determined potentiometrically.

Individual second-order rate constants, k_2, were calculated as described above. The average k_2 was obtained from a minimum of eight individual k_2 values for each substrate with no one k_2 value deviating from another by more than 4%. The reactions were followed to 55–65% of the half-lives. The values so obtained (at 20°) are given in Table I.

With Sodium Iodide. Initial concentrations of iodide ion and substrate in acetone were equal in all cases (0.050 M). Ten milliliters each of iodide and of substrate solutions were pipetted into 180 ml of acetone at 20 °C to yield an overall concentration of 0.050 M in each reactant. The reaction was quenched by discharging 10 ml of the re-

action mixture into a 250-ml separatory funnel containing 80 ml of water and 100 ml of ether. The ether layer was extracted twice with water and the water extracts were combined. The aqueous layer was then titrated potentiometrically for iodide ion content. Occasionally the iodide ion was checked with the chloride ion liberated, and excellent agreement was obtained.

Individual second-order rate constants, k_2, were calculated as described above. The average k_2 was obtained from a minimum of nine individual k_2 values for each substrate with no one k_2 value deviating from another by more than 3%. The reactions were followed to 55–65% of the half-lives. The values so obtained are presented in Table I.

Reaction Products. Adequate representative product studies were done by Bunnett[3] and by Reinheimer[5] with various ortho- and para-substituted benzyl chlorides and each of the nucleophiles employed.

Registry No.—LiOMe, 865-34-9; LiSPh, 2973-86-6; NaI, 7681-82-5; MeOH, 67-56-1; *p*-methylbenzyl chloride, 26519-66-4; *p*-chlorobenzyl chloride, 104-82-5; *p*-bromobenzyl chloride, 589-17-3; *p*-iodobenzyl chloride, 54589-53-6; *o*-methylbenzyl chloride, 552-45-4; *o*-chlorobenzyl chloride, 611-19-8; *o*-bromobenzyl chloride, 578-51-8; *o*-iodobenzyl chloride, 59473-45-9.

References and Notes

(1) K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959); E. S. Lewis and H. Suhr, *ibid.*, **82** 862 (1960); E. Spinner, *Aust. J. Chem.*, **13**, 218 (1960); H. D. Holtz and L. M. Stock, *J. Am. Chem. Soc.*, **87**, 2404 (1965); A. J. Sisti and W. Memeger, Jr., *J. Org. Chem.*, **30**, 2102 (1965); R. A. Abramovitch and J. A. Newman, Jr., *ibid.*, **39**, 2690 (1974); R. F. Hudson, *Chimia*, **16**, 173 (1962).

(2) J. F. Bunnett, *J. Am. Chem. Soc.*, **79**, 5969 (1957).

(3) J. F. Bunnett and J. D. Reinheimer, *J. Am. Chem. Soc.*, **84**, 3284 (1962).

(4) A. J. Sisti and S. Lowell, *J Org. Chem.*, **29**, 1635 (1964).

(5) D. Dalrymple, J. Reinheimer, D. Barnes, and R. Baker, *J. Org. Chem.*, **29**, 2647 (1964).

(6) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 649.

(7) One may argue that the $k_o:k_p$ rate ratios for I^- may be altered due to the solvent change indicated and thus the trends in the values of the $k_o:k_p$ rate ratios for a given substituent with different nucleophiles may be altered so that no need arises for the consideration of any new factor(s). However, the trends in the $k_o:k_p$ values with different substituents for a given nucleophile (examine the table horizontally) in a given solvent cannot be explained because of a solvent change or steric and electrical considerations (see also ref 8).

(8) Recently, M. Charton [*J. Am. Chem. Soc.*, **91**, 6649 (1969)] has offered evidence that the electrical effect of a substituent from the ortho and para positions is not the same and, therefore, it may be reasonably argued that the increasing trends in the $k_o:k_p$ rate ratios ($MeO^- \rightarrow I^-$) for a given substituent can be attributed to the different responses of each nucleophile to this electrical difference, the latter, instead of coulombic interactions between the nucleophile and the ortho substituent, being the factor offsetting the steric effect. However, two arguments can demonstrate that all the observed trends in the $k_o:k_p$ rate ratios cannot be explained because of this electrical difference. First, since it is known that PhS^- and I^- respond more[5,20] favorably to the electron-withdrawing para halogens (relative to hydrogen) than to the electron-donating *p*-methyl group (relative to hydrogen), the $k_o:k_p$ rate ratios for the chloro and bromo groups should be larger than for the methyl group as a result of steric considerations and any electrical difference from the two positions (the substituent's electrical effect is assumed greater at the ortho position). The latter conclusion is contrary to the experimental results. Second, since any electrical difference between *o*-Cl and *p*-Cl, *o*-Br and *p*-Br, and *o*-I and *p*-I groups should be essentially the same, $(\sigma_p - \sigma^*_o)_X \simeq$ constant (ref 6, p 591), the response of a given nucleophile to the same electrical difference should be identical and is, therefore, incorporated in each of the $k_o:k_p$ values to the same extent. The effect then of any electrical difference from the two positions on the $k_o:k_p$ values for the different halo groups with a given nucleophile (examine Table II horizontally) has been cancelled or accounted for.

(9) Values taken from Landolt-Bronstein and J. A. A. Ketelaar, "Chemical Constitution", 2d ed, American Elsevier, New York, N.Y., 1958, pp 91 and 201.

(10) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

(11) These interactions should also occur between the leaving group and a given ortho substituent. Since these forces should occur in the ground state and the transition state, their effect on the $k_o:k_p$ rate ratio will be determined by whether the difference favors the transition state or the ground state. The difference should favor the transition state because both μ_{C-Cl} and α_{Cl} should be larger in the transition state. However, whatever the increment in the $k_o:k_p$ rate ratio as a result of these interactions, it should be the same for each nucleophile with a given ortho substituent.

(12) It is difficult to qualitatively determine the relative centers of negative charge, q_N, in the transition state involving nucleophiles of different polarizabilities and different N · · · C bond lengths and, therefore, difficult to assess the relative distances, *r*, between q_N and the ortho substituent. This force is thus assumed to be essentially the same for each nucleophile with a given ortho substituent (*r* is essentially the same for each nucleophile).

(13) As mentioned in ref 11, these interactions also obtain between the leaving group and *o*-halo substituents and should occur in the ground state as well as the transition state. However, with different $\alpha_{o\text{-sub}}$ the magnitude of the difference favoring the transition state (see ref 11) will not be the same for any given nucleophile. The difference favoring the transition state should become larger as the $\alpha_{o\text{-sub}}$ increases and will also offset the increasing steric effect (Cl to I).

(14) Similarly, the same conclusion would result from consideration of the varying steric effect of the methyl and halo groups together with the coulombic interactions (thus far discussed) between the leaving group and *o*-halo and *o*-methyl groups. The difference between the leaving group–ortho-substituent interactions in the ground state and transition state favors the latter and should become larger as the $\alpha_{o\text{-sub}}$ increases (see ref 11 and 13).

(15) These additional interactions should also occur between the leaving group and the *o*-methyl group. Since these additional forces should occur in the ground state and the transition state, their effect on the $k_o:k_p$ rate ratio will be determined by whether the difference favors the transition state or the ground state. The difference should favor the transition state because both μ_{C-Cl} and α_{Cl} should be larger in the transition state. However, whatever the increment in the $k_o:k_p$ rate ratio as a result of these interactions, it should be the same for each nucleophile.

(16) Unpublished results with neutral nucleophiles of low polarizabilities (pyridine and diethyl sulfide) lend support to the operation of these additional forces involving the *o*-methyl dipole and the dipole and charge of the nucleophile. The neutral nucleophiles gave values for the $k_o:k_p$ rate ratios which were completely opposite to those herein, i.e., the values were higher for all the halo groups relative to the methyl group. The force deemed responsible is the intermediate range, ion_N–$dipole_{o\text{-halo group}}$, which in this case favors the halogens because of the favorable disposition of its dipole (+ ← X) to the positive charge generated in the transition state with neutral nucleophiles. With nucleophiles of low polarizability the $dipole_N$–$dipole_{o\text{-}CH_3}$ and $dipole_{o\text{-}CH_3}$–induced $dipole_N$ interactions will be small (μ_N and α_N small) compared to the ion_N–$dipole_{o\text{-halo group}}$.

(17) The model for the transition state structure used for all the substituents throughout the discussion may be considered inadequate since no consideration was given to loose and tight transition state structures [A. J. Parker, *Chem. Rev.*, **69**, 1 (1969)]. Including consideration of variations in looseness and tightness of the transition state structures, the favorable coulombic interactions discussed together with the steric effect (benzyl hydrogen and ortho substituent, Chart Ia) can still explain all the trends in the $k_o:k_p$ rate ratios. Whether the electrical effect of the substituent promotes a loose (methyl group) or tight (halo groups) transition state structure its effects will cancel in the $k_o:k_p$ rate ratio for a given substituent with a given nucleophile. However, the looseness or tightness of the transition state structures should vary with the nucleophile used for a given substituent. This change in looseness or tightness with the nucleophile employed will only affect the size of the coulombic interactions between the different nucleophiles and a given ortho substituent (compared to the model used, Chart I) and not the trends expected from these interactions with the different nucleophiles and a given ortho substituent (no matter how the transition states differ in looseness or tightness for the three nucleophiles, the order of α and μ is I > PhS > MeO).[12] The coulombic forces between a given ortho substituent and the leaving group will not be the same for each of the nucleophiles[11] but will increase (compared to the model used, Chart I) as the looseness (methyl group) increases and as the tightness (halo groups) decreases in the transition state structure for the three nucleophiles since α_{Cl}, μ_{Cl}, and q_{Cl} would become accordingly larger. Since it is not obvious how the three nucleophiles vary in looseness or tightness for a given ortho substituent the trend for the latter increasing coulombic interactions with the nucleophiles cannot be indicated. The effect of the looseness or tightness of the transition state structure on the coulombic interactions between a given nucleophile with different ortho substituents must also be considered when comparing the $k_o:k_p$ rate ratios for the methyl group (loose transition state structure) with those for the halo groups (tight transition state structures). The loose transition state structure would favor all the coulombic interactions between the *o*-methyl group with both a given nucleophile and leaving chloride even more than in the model employed (Chart I) because in the loose transition state structure the *q*, α, and μ for any given nucleophile and for the leaving chloride would be larger than either in the model used or in the tight transition state structure. In the $k_o:k_p$ rate ratios for the halogen compounds with a given nucleophile the tightness of the transition state structures will result in a decrease in q_N, α_N, and μ_N (compared to the model employed). The latter will cause a lessening in the size of the increasing coulombic forces[13] ascribed to offsetting the increasing steric effect (Cl to I).

As assumed steric interaction between the nucleophile and ortho substituent should make the transition state structure looser for the *o*-methyl compound compared to the transition state structure for the *p*-methyl compound and the transition state structures for the *o*-halo compounds not as tight compared to the transition state structures for the *p*-halo compounds (reference above). Arguments can be presented to show that if the difference in looseness (methyl group) and the difference in tightness between the transition state structures for the ortho compound and para compound is assumed the favorable factor offsetting the steric effect, it cannot account for all the trends in the $k_o:k_p$ rate ratios.

(18) All melting points and boiling points are uncorrected. All liquid benzyl chlorides were distilled using a 60 cm helix column. All organic compounds were used within 24 h after purification. Each of the benzyl chlorides was tested for purity by VPC and were thereby shown to be at least 99% pure.

(19) S. Oliver and A. Weber, *Recl. Trav. Chim. Pays-Bas*, **41**, 307 (1922).

(20) G. M. Bennett and B. Jones, *J. Chem. Soc.*, 1815 (1935).

(21) G. L. Goerner and R. C. Nanetz, *J. Am. Chem. Soc.*, **73**, 2940 (1951).

(22) M. S. Newman, *J. Am. Chem. Soc.*, **62**, 2295 (1940).

(23) N. A. Lange, "Handbook of Chemistry", 9th ed, Handbook Publishers, Sandusky, Ohio, 1956, p 693.

(24) C. G. Swain and W. P. Langsdorf, Jr., *J. Am. Chem. Soc.*, **73**, 2813 (1951).

Synthesis and Utilization of Organocopper(I) Ate Complexes from Grignard Reagents

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Organocopper(I) ate complexes can be prepared in high yield from methylcopper(I) and aliphatic or aryl Grignard reagents. The resulting complexes efficiently transfer the Grignard reagent derived primary, secondary, tertiary, or aryl group in reactions in acyl chlorides leading to ketones. This synthetic method is illustrated with procedures for $CH_3(CH_2)_{15}COCH_3$, $C_6H_5COC_6H_5$, $CH_3(CH_2)_2CH(CH_3)COCH_3$, $(CH_3)_3CCOC_6H_5$, p-$CH_3C_6H_4COC_6H_5$, $C_6H_5COCH_3$, $(CH_3)_3CCOC(CH_3)_3$, and $C_6H_5CO(CH_2)_3CH_3$. This reaction provides a general and useful alternative to syntheses of organocopper(I) ate complexes from organolithium reagents. Methylcopper(I) is shown to be significantly better than other copper(I) species for forming reactive organocopper(I) ate complexes from Grignard reagents.

Applications of organocopper(I) reagents in organic synthesis have expanded in recent years to include numerous alkylation reactions such as alkylation of alkyl halides, acyl halides, and α-halogenated carbonyl compounds.[1] These reactions and the well-established 1,4-conjugate addition of organocopper reagents to α,β-unsaturated carbonyls[2] make organocopper reagents versatile synthetic intermediates.[3] However, the principal synthetic route to reactive organocopper(I) ate complexes is still the reaction of an alkyllithium reagent with a free or complexed copper(I) salt. In general, the more readily available Grignard reagents cannot be used in place of an alkyllithium reagent in these syntheses.[1,4] Other routes to reactive organocopper(I) compounds from organomercurials[5] and organoboranes[6] have recently been reported, but these methods are not as generally applicable as the reaction of organolithium reagents with copper(I) salts.

We wish to report a useful alternative to the above syntheses that employs the reaction of a Grignard reagent with preformed methylcopper(I) to generate an organocopper(I) ate complex capable of selectively transferring the Grignard reagent derived alkyl group in synthetically useful reactions. The utility of these Grignard reagent derived organocopper(I) reagents in the synthesis of ketones from acid chlorides is described.[7] We have also comparatively evaluated routes leading to reactive organocopper(I) reagents from copper(I) species other than methylcopper(I).

Results

Methylcopper(I), prepared from a THF suspension of cuprous iodide and methyllithium, reacts in high yield (vide infra) with Grignard reagents to give organocopper(I) ate complexes. These complexes can be formed equally well from primary, secondary, tertiary, and aryl Grignard reagents. The organocopper(I) ate complexes so formed have been demonstrated to have useful reactivity toward acyl halides, alkyl halides,[8] and α,β-unsaturated ketones.[9] Representative examples of the reaction of these ate complexes with acyl chlorides leading to ketones are detailed in Table I.

In a typical procedure, 50 mmol of preformed methylcopper(I) in 150 ml of THF was allowed to react with 50 mmol of *tert*-butylmagnesium bromide at −78 °C to yield, after warming to 25 °C, a suspension of an organocopper(I) ate complex. Addition of 50 mmol of benzoyl chloride by syringe to this purple suspension of *tert*-butyl(methyl)copper(I) magnesium bromide[10] at −78 °C gave a yellow suspension. After warming to room temperature and stirring for 1 h, workup (see Experimental Section) and simple distillation yielded 97% of ketone product which was a mixture of acetophenone (10%) and pivaloylphenone (90%).

As can be seen from the data in Table I, it is possible to achieve significant selectivity in the transfer of the alkyl group originally bound to magnesium if the aklylation reaction is carried out at −78 °C with stoichiometric amounts of acyl chloride and copper reagent. However, since the by-product resulting from transfer of a methyl group can often be easily separated from the desired product, excess acyl chloride can be used in many cases to ensure complete reaction. Steric factors in the acyl chloride or organocopper(I) ate complex also appear to be unimportant in this reaction as demonstrated by the comparable yields of acetophenone, 2,2-dimethyl-1-phenyl-1-propanone, and 2,2,4,4-tetramethyl-3-pentanone.

These Grignard reagent derived organocopper(I) ate complexes are qualitatively different from their lithium diorganocuprate analogues in several respects. First, although the magnesium containing ate complexes are soluble as dilute (ca. 0.2 M) solutions at 25 °C, they form suspensions at −78 °C in contrast to lithium dialkylcuprates. Second, the thermal stability of magnesium containing ate complexes is somewhat greater than that of corresponding lithium diorganocuprates. For example, lithium di-*tert*-butylcopper(I) decomposes on warming to 25 °C[11] while *tert*-butyl(methyl)copper(I) magnesium bromide is stable for at least 30 min at 25 °C. Although the reason for this slightly greater thermal stability is unknown, it is worthwhile to note that incorporation of a methyl group into lithium dialkylcuprates enhances the thermal stability of the resulting lithium dialkylcuprate.[12] The observation that ternary copper(I) ate complexes containing mercury(II) have enhanced thermal stability suggests that the magnesium may also be important in increasing the thermal stability of these ate complexes.

The selectivity in the transfer of the alkyl groups observed in these reactions parallels that observed in alkylation reactions of these ate complexes with alkyl halides.[8] Comparable selectivity has been observed with lithium methyl(vinyl)copper(I) in 1,4-conjugate addition reactions suggesting that this preference for transfer of alkyl groups other than methyl may be general.[13,14]

It is evident from the isolated and GLC measured yields that this procedure is comparable to the synthesis of ketones from acid chlorides and lithium diorganocuprates. Since Grignard reagents are more readily available than alkyllithium reagents, this synthesis represents a reasonable alternative route to ketones from carboxylic acid chlorides. The procedure is also compatible with a variety of functional groups, as demonstrated by the stability of methyl benzoate and acetophenone to *n*-butyl(methyl)copper(I) magnesium bromide under the reaction conditions (see Experimental Section). A further advantage of these procedures is that high yields can be obtained without the necessity for excess reagents. A limitation of this procedure is that the formation of the by-

Table I. Ketones Synthesized from Grignard Reagents Using Organocopper(I) Ate Complexes "$R(CH_3)CuMgX$" and Acyl Chlorides

Grignard reagent (R)	Registry no.	Acyl halide	Registry no.	Product	Registry no.	Isolated yield, %[a]
$CH_3(CH_2)_{14}CH_2MgBr$	112-82-3	CH_3COCl	75-36-5	$CH_3(CH_2)_{15}COCH_3$	7373-13-9	75
$CH_3CH_2CH_2CH_2MgBr$	109-65-9	C_6H_5COCl	98-88-4	$CH_3(CH_2)_3COC_6H_5$	1009-14-9	85[b]
$CH_3(CH_2)_2CH(CH_3)MgBr$	107-81-3	CH_3COCl		$CH_3(CH_2)_2CH(CH_3)COCH_3$	2550-21-2	90
$(CH_3)_3CMgBr$	507-19-7	C_6H_5COCl		$(CH_3)_3CCOC_6H_5$	938-16-9	93[b]
p-$CH_3C_6H_4MgBr$	106-38-7	C_6H_5COCl		p-$CH_3C_6H_4COC_6H_5$	134-84-9	79
C_6H_5MgBr	108-86-1	$(CH_3)_3CCOCl$	3282-30-2	$C_6H_5COC(CH_3)_3$		100[c]
$(CH_3)_3CMgBr$		$(CH_3)_3CCOCl$		$(CH_3)_3CCOC(CH_3)_3$	815-24-7	90[d]
C_6H_5MgBr		CH_3COCl		$C_6H_5COCH_3$	98-86-2	84
C_6H_5MgBr		C_6H_5COCl		$C_6H_5COC_6H_5$	119-61-9	96[c]

[a] These yields are based on Grignard reagent. The product ketones were identified by their physical (melting point, boiling point) and spectroscopic properties (ir, NMR). In all cases, gas chromatography showed the isolated products to be >98% pure. Isolated ketones were also characterized by formation of a 2,4-dinitrophenylhydrazone or semicarbazone derivative. [b] One equivalent of acyl chloride per equivalent of Grignard reagent was used to minimize formation of acetophenone. [c] Yield determined by gas chromatography. [d] The isolation of pure product in this example was hampered by co-distillation of pinacolone.

Table II. Utility of Copper(I) Compounds, RCu, in Forming Reactive Ate Complexes with *n*-Butylmagnesium Bromide

RCu	Registry no.	Yield of ketone product after reaction with benzoyl chloride, %[a]	Reactivity toward methyl benzoate at 25 °C (% methyl benzoate recovered)
$(CH_3)_3$-CC≡CCu	40575-23-3	28 (74)[b]	99
$(CH_3)_3COCu$	35342-67-7	0[c] (94)[b]	102
C_6H_5SCu	1192-40-1	0[c] (79)[b,d]	101
ICu	7681-65-4	46[e]	45[e]
CH_3Cu	1184-53-8	85[d]	100

[a] Yields determined by GLC under comparable conditions using octadecane as an internal standard. These yields are based on the assumption that only one alkyl group can be transferred per copper atom. [b] This yield was obtained using *n*-butyllithium instead of *n*-butylmagnesium bromide. [c] No 1-phenyl-1-pentanone was detected by GLC. [d] This is an isolated yield. [e] The presence of a dark suspension suggested that decomposition of the organocopper(I) had occurred under the reaction conditions.

product methyl ketone cannot be completely suppressed and the separation of small amounts of methyl ketone from the product of interest may be difficult in some cases.

Because of the conflicting reports in the literature concerning the efficacy of Grignard reagents for the synthesis of reactive organocopper(I) compounds, we briefly examined the use of starting copper(I) species other than methylcopper(I). The results of these studies are listed in Table II. As can be seen from the stability of methyl benzoate under comparable conditions, an equilibrium concentration of Grignard reagent is not present in any of these cases. This implies complex formation. Nonetheless, reaction of these complexes with benzoyl chloride under comparable conditions to those discussed above leads to significantly lower yields of ketone product. The lower reactivity for *n*-butyl-(3,3-dimethylbutynyl)-, *n*-butyl(*tert*-butoxy)-, and *n*-butyl(thiophenoxy)copper(I) magnesium bromide relative to *n*-butyl(methyl)copper(I) magnesium bromide is in accord with previous studies of the relative reactivities of mixed lithium cuprates.[14]

Conclusion

Reaction of methylcopper(I) with a wide variety of Grignard reagents leads to organocopper(I) ate complexes whose reactivity is comparable to that of lithium diorganocuprates. These Grignard reagent derived cuprates have been shown to be effective in alkylation of alkyl halides and in alkylation of acyl chlorides to yield ketones. These Grignard reagent derived cuprates show both useful selectivity and efficiency in their reactions, transferring the alkyl group originally bound to magnesium preferentially and in high yield without the need for excess reagent. In addition, the thermal stability of these "alkyl(methyl)copper(I) magnesium halide" reagents is somewhat greater than that of their lithium dialkylcopper(I) analogues. Methylcopper(I) is also shown to be the most useful copper(I) species for the formation of reactive organocopper(I) reagents from organomagnesium compounds.

Experimental Section

General Methods. All reactions of air and water sensitive organometallics were carried out in flame-dried glassware under prepurified nitrogen using standard techniques.[15] Tetrahydrofuran and other ethereal and hydrocarbon solvents were distilled from a purple solution or suspension of disodium benzophenone dianion prior to use. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60 spectrometer. Infrared spectra were taken on sodium chloride plates or in sodium chloride cells on a Beckman IR-8 spectrometer. A Perkin-Elmer Model 3920 gas chromatograph was used for GLC analyses. A 0.32 by 183 cm 3% SP-2300 on 100/120 Supelcoport column was used for both qualitative and quantitative analyses. Lithium reagents were purchased from Alfa Inorganics Inc. Lithium reagents and Grignard reagents were analyzed by the method of Watson and Eastham.[16] When the difference between total base as determined by titration with standard 0.1 M HCL and active organometallic exceeded 10% of the active organometallic, the solutions were discarded. 1-Bromohexadecane was purchased from Air Products and Chemicals. Other organic chemicals were purchased from the Aldrich Chemical Co. Acid chlorides were redistilled prior to use. Magnesium turnings for the preparation of Grignard reagents were purchased from Fisher Scientific. Cuprous iodide was generally purified prior to use[17] although freshly opened bottles were also found to be satisfactory.

3,3-Dimethylbutyne was prepared in 90% yield according to the procedure of Collier and Macomber.[18]

General Procedure for the Synthesis of Ketones as Illustrated by the Synthesis of 4-Methylbenzophenone. 4-Methylphenylmagnesium bromide was prepared from magnesium turnings and 4-methylbromobenzene in ether using standard procedures. A bright yellow suspension of methylcopper(I) was prepared in a 1-l., flame-dried, three-necked, round-bottomed flask equipped with an overhead stirrer and low-temperature thermometer by the reaction of 30 ml of a 1.73 N (51.9 mequiv) ether solution of methyllithium (0.11 N in

residual base) with a −78 °C suspension of 9.6 g (50.8 mmol) of cuprous iodide in 100 ml of THF. The bright yellow color characteristic of methylcopper(I) formed when this reaction mixture was warmed to 25 °C. After this yellow suspension was cooled to −70 °C with a dry ice–acetone bath, 26 ml of a 1.96 N (51.0 mequiv) ether solution of 4-methylphenylmagnesium bromide was added with a syringe. The resulting suspension was allowed to warm to 25 °C with stirring after removal of the dry ice–acetone bath. The resulting deep purple solution was cooled to −78 °C and 13 ml (112 mmol) of benzoyl chloride in 30 ml of THF was added dropwise by syringe. The reaction mixture was then warmed to 25 °C with stirring and allowed to stir for an additional 0.5 h. Addition of 8 ml of absolute methanol quenched any unreacted organometallic and benzoyl chloride. The reaction mixture was then added to 600 ml of saturated aqueous ammonium chloride solution. Stirring this mixture for 2 h dissolved any copper salts and facilitated the subsequent extractions.[19] The ethereal phase was then separated and the aqueous portion was washed with two 100-ml portions of ether. The combined organic fractions were washed once with 100 ml of 0.1 N aqueous sodium thiosulfate, three times with 100 ml of 1.0 N sodium hydroxide, and once with 200 ml of saturated sodium chloride, and then dried (K_2CO_3). The product 4-methylbenzophenone was isolated (7.8 g, 79% yield) by distillation using a short-path distillation apparatus and had bp 120–130 °C (0.6 Torr) [lit.[20] bp 311–312 °C (720 Torr)]; ir (CH_2Cl_2) 1670 cm^{-1}; NMR ($CDCl_3$) δ 7.1–7.9 (m, 9 H), 2.4 (s, 3 H). The 2,4-dinitrophenylhydrazone of this product had mp 198–199 °C (lit.[20] mp 199–200 °C).

1-Phenyl-1-pentanone was prepared from *n*-butylmagnesium bromide according to the procedures described above with the slight modification that only 1 equiv of benzoyl chloride per equivalent of starting Grignard reagent was used to minimize acetophenone formation. The product 1-phenyl-1-pentanone was purified by fractional distillation through a 50 by 1 cm Holtzman column packed with a spiral wire and was isolated in 85% yield: bp 146–150 °C (38 Torr) [lit.[20] bp 135–140 °C (25 Torr)]; ir (neat) 1690 cm^{-1}; NMR (CCl_4) δ 7.1–8.0 (m, 5 H), 2.56 (t, 2 H), 1.0–2.0 (m, 4 H), 0.97 (t, 3 H). A 2,4-dinitrophenylhydrazone derivative prepared from the purified product had mp 163–164 °C dec after several recrystallizations from 95% ethanol (lit.[20] mp 166 °C). Gas chromatography showed that the distilled product contained less than 5% acetophenone as the only impurity.

3-Methyl-2-hexanone, prepared from 2-pentylmagnesium bromide according to the procedure described above, was isolated in 90% yield (5.1 g) after distillation and had bp 142–146 °C (lit.[20] bp 142–145 °C); ir (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.47 (m, 1 H), 2.05 (s, 3 H), 0.9–1.8 (m, 4 H), 1.03 (d, 3 H), 0.93 (t, 3 H).

2-Octadecanone. Following the general procedures described above, hexadecylmagnesium bromide and methylcopper(I) were allowed to react to give an ate complex which was then allowed to react with excess acetyl chloride to give 20 g (75%) of 2-octadecanone which was isolated as a pure product after recrystallization from ethanol. The product 2-octadecanone had mp 49–50 °C (lit.[20] mp 52 °C) and ir (CCl_4) 1711 cm^{-1}. The identity of the product was confirmed by preparation of a semicarbazone derivative having mp 124–125 °C (lit.[20] mp 125.5–126 °C).

2,2-Dimethyl-1-phenyl-1-propanone was prepared from *tert*-butylmagnesium bromide and benzoyl chloride as described above. Traces of acetophenone in the distilled ketone product were removed by column chromatography using silica gel. The product ketone had bp 216–220 °C (lit.[20] bp 219–221 °C); ir (neat) 1682 cm^{-1}; NMR (neat) δ 7.1–8.0 (m, 5 H), 1.27 (s, 9 H). The product was further characterized by the preparation of a 2,4-dinitrophenylhydrazone derivative having mp 192–193 °C dec (lit.[20] mp 194 °C).

This ketone was also prepared on a 1-mmol scale from phenylmagnesium bromide and pivaloyl chloride following similar procedures. Analysis by GLC using nonadecane as an internal standard showed that 2,2-dimethyl-1-phenyl-1-propanone had been formed in quantitative yield.

2,2,4,4-Tetramethyl-3-pentanone was prepared on a 1-mmol scale from *tert*-butylmagnesium bromide and pivaloyl chloride according to the procedure described above in 90% yield as determined by gas chromatography using *n*-decane as an internal standard.

Benzophenone was prepared from phenylmagnesium bromide and benzoyl chloride according to the procedures described above. Gas chromatographic analysis of a 1-mmol scale reaction using *n*-docosane as an internal standard showed that the product ketone had formed in 96% yield.

Acetophenone was prepared from phenylmagnesium bromide and acetyl chloride according to the procedure described above. The product acetophenone was isolated by distillation in 83% yield and had bp 200–204 °C (lit.[20] bp 202 °C); ir (neat) 1691 cm^{-1}; NMR ($CDCl_3$) δ 7.2–8.0 (m, 5 H), 2.50 (s, 3 H); 2,4-dinitrophenylhydrazone mp 241–242 dec (lit.[20] mp 237 °C).

Evaluation of Other Copper(I) Salts in the Synthesis of Reactive *n*-Butylcopper(I) Ate Complexes. Cuprous thiophenoxide, cuprous *tert*-butoxide, and 3,3-dimethylbutynylcopper(I) were prepared according to literature procedures.[7,14] One equivalent of 1.55 N *n*-butylmagnesium bromide in ether per equivalent copper(I) salt was added to a −78 °C suspension of the copper(I) species. Warming to room temperature then generated the butylcopper(I) ate complex of interest. The *n*-butyl(thiophenoxy)copper(I) magnesium bromide was a white suspension, the *n*-butyl(*tert*-butoxy)copper(I) magnesium bromide was a blue solution, the *n*-butyl(3,3-dimethylbutynyl)copper(I) magnesium bromide was a greenish solution, and the di-*n*-butylcopper magnesium bromide was a dark gray suspension. The reactivity of these resulting complexes was evaluated by addition of excess benzoyl chloride and subsequent GLC analysis for 1-phenyl-1-pentanone. Results of these experiments are detailed in Table II.

In similar experiments. the stability of methyl benzoate in the presence of these mixed ate complexes was evaluated by addition of a known amount of methyl benzoate and an internal GLC standard to the organometallic solution or suspension of interest. The stability of methyl benzoate to these various complexes is described in Table II and was determined by gas chromatography.

Stability of methyl benzoate and 1-phenyl-1-pentanone to *n*-butyl(methyl)copper(I) magnesium bromide was determined by the addition of known amounts of these compounds and appropriate internal standards to the ate complex formed by reaction of *n*-butylmagnesium bromide with methylcopper(I). These reaction mixtures were stirred for 1 h at −78 °C and 1 h at 25 °C. The organometallic species present was then quenched with methanol and the yield of recovered ketone or ester was determined by GLC. In several separate runs, both methyl benzoate and 1-phenyl-1-pentanone could be recovered in yields ranging from 94 to 100%.

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Registry No.—Methyl benzoate, 93-58-3; hexadecyl(methyl)copper(I) magnesium bromide, 59547-38-5; *n*-butyl(methyl)copper(I) magnesium bromide, 59532-66-0; 2-pentyl(methyl)copper(I) magnesium bromide, 59532-64-8; *tert*-butyl(methyl)copper(I) magnesium bromide, 59532-65-9; 4-methylphenyl(methyl)copper(I) magnesium bromide, 59532-62-6; phenyl(methyl)copper(I) magnesium bromide, 59532-63-7; *n*-butyl(thiophenoxy)copper(I) magnesium bromide, 59532-67-1; *n*-butyl(*tert*-butoxy)copper(I) magnesium bromide, 59532-60-4; *n*-butyl(3,3-dimethylbutynyl)copper(I) magnesium bromide, 59532-59-1; di-*n*-butylcopper magnesium bromide, 59532-61-5.

References and Notes

(1) G. H. Posner, *Org. React.*, **22**, 253 (1975).
(2) G. H. Posner, *Org. React.*, **19**, 1 (1972).
(3) Other reviews detailing synthetic applications of organocopper chemistry include A. E. Jukes, *Adv. Organomet. Chem.*, **12**, 215 (1974); J. F. Normant, *Synthesis*, 63 (1972); and G. Bahr and P. Burba in "Methoden der Organischen Chemie", Vol. 13, 4th ed, E. Müller, Ed., Georg Theime Verlag, Stuttgart, 1970, p 735.
(4) L. M. Seitz and R. Madl, *J. Organomet. Chem.*, **34**, 415 (1972); G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Am. Chem. Soc.*, **91**, 4871 (1969).
(5) D. E. Bergbreiter and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 4937 (1974).
(6) Y. Yamamoto, H. Yatagai, and I. Moritani, *J. Am. Chem. Soc.*, **97**, 5606 (1975).
(7) For a summary of other comparable routes to ketones, see L. S. Hegedus, P. M. Kendall, S. M. Lo, and J. R. Sheats, *J. Am. Chem. Soc.*, **97**, 5448 (1975); G. H. Posner, C. E. Whitten, and J. J. Sterling, *ibid.*, **95**, 7788 (1973); and N. T. Luong-Thi, H. Rivieré, J. Bérgue, and C. F. Forester, *Tetrahedron Lett.*, 2113 (1971).
(8) D. E. Bergbreiter and G. M. Whitesides, *J. Org. Chem.*, **40**, 870 (1975).
(9) Copper(I) salts are known to be effective catalysts for 1,4-conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds.[2] As expected, methylcopper(I) behaves in a similar fashion.
(10) For convenience, we have named these ate complexes according to the stoichiometry involved in their formation. The actual structure and extent of aggregation of these complexes is not known.
(11) Significant amounts of decomposition were suggested by the variable amounts of ketone products formed upon reaction with benzoyl chloride (typical yields of pivaloylphenone ranged from 10 to 40%).
(12) D. E. Bergbreiter, unpublished observations.
(13) H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, **40**, 1460 (1975).

(14) Alkyl groups other than methyl show significantly less selectivity in transfer of one particular alkyl group in mixed lithium dialkyl cuprates; cf. W. H. Mandeville and G. M. Whitesides, *J. Org. Chem.*, **39**, 400 (1974).
(15) H. C. Brown, "Organic Syntheses via Boranes", Wiley, New York, N.Y., 1975.
(16) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
(17) R. N. Keller and H. D. Wycoff, *Inorg. Synth.*, **2**, 1 (1946).
(18) W. L. Collier and R. S. Macomber, *J. Org. Chem.*, **38**, 1369 (1973).
(19) When excess acid chloride is used, addition of a few pellets of sodium hydroxide helps dissolve the copper salts.
(20) J. R. A. Pollock and R. Stevens, Ed., "Dictionary of Organic Compounds", Oxford University Press, London, 1965.

Methylation of Thioanisoles and Anilines by 1-Methyl-2,5-diphenyl-1,4-dithiinium Tetrafluoroborate. Kinetics and Correlations[1]

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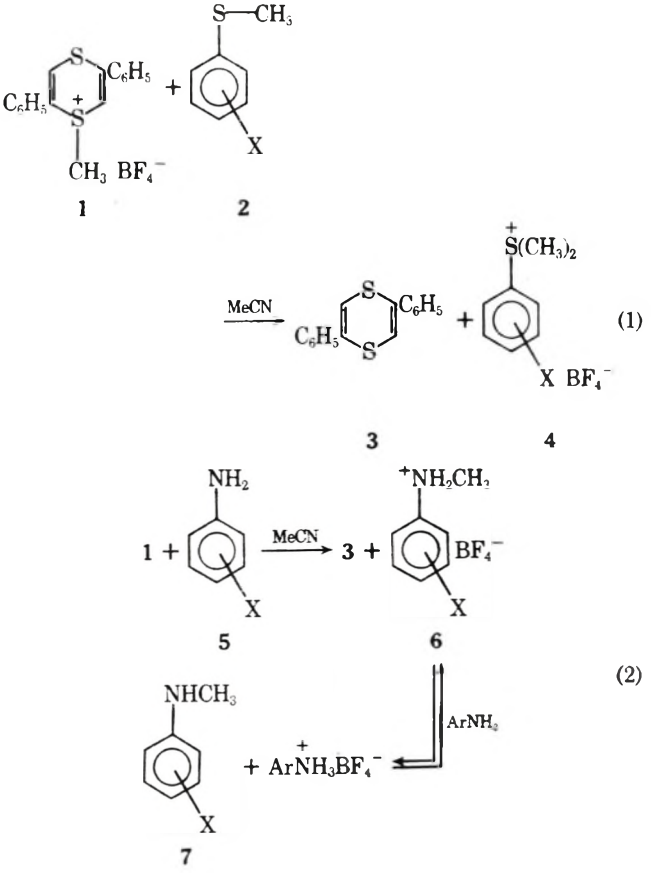
The kinetics of methyl transfer from 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (**1**) to a series of thioanisoles (**2**) and to a comparable series of anilines (**5**) have been followed spectrophotometrically in acetonitrile under pseudo-first-order conditions at four temperatures for each compound. Derived second-order rate constants, Arrhenius equation constants, and activation thermodynamic parameters have been calculated for intra- and inter-series comparison. Both series exhibited well-defined Hammett correlations ($\rho_S = -1.58 \pm 0.04$; corr coeff = 0.999 for the thioanisoles, and $\rho_N = -1.95 \pm 0.05$; corr coeff = 0.998 for the anilines) in which the ρ values were essentially constant over the range 25–80 °C. Specific rate constants for the thioanisole set (k_S^X) correlated well with those of the aniline set (k_N^X) via a linear equation: $\log k_S^X = m \log k_N^X +$ constant, where the slope m is approximated by the ratio of Hammett ρ values (ρ_S/ρ_N). Comparisons with literature data show that dimethyl sulfate is 2.3 times as reactive as **1** toward the thioanisoles, and that **1** is about 10 times as reactive as MeI toward the anilines.

Transmethylation reactions,[3,4] which play a normal role in the cobalamin-dependent biosynthesis of methionine[5] and in the transfer of intact methyl groups from *S*-adenosyl-L-methionine to various receptor substrates,[6] appear to be universally important in biological systems. In addition to the enzyme specificities involved, such reactions apparently depend upon a subtle interplay of relative nucleophilicities of nitrogen, sulfur, oxygen, and cobalt moieties which are not yet well understood. The very concept of nucleophilicity, considered as kinetic basicity, has defied precise quantification and various equations in the literature have been shown to be of limited value for predicting relative nucleophilic reactivity.[7] Some qualitative comparisons of the relative nucleophilicities of S, N, and Co in methyl transfers have been reported by Schrauzer[8] who used simple methylsulfonium, -ammonium, and -cobaloxime models. More recently, Coward and Sweet[9] provided the first detailed kinetic study of methyl transfer from substituted aryldimethylsulfonium perchlorates to various anionic and amine nucleophiles.

In our laboratory we have been particularly interested in the nucleophilicity of bivalent sulfur. Qualitatively, it is well known that simple dialkyl sulfides are easily methylated by methyl iodide, sulfate, or sulfonates to give the corresponding sulfonium salts.[10] Compounds such as thioanisole (**2**, X = H) or diphenyl sulfide, in which bivalent sulfur is bonded to one or two sp^2 carbons, are alkylated with more difficulty, requiring either methyl sulfate at elevated temperatures or methyl iodide in the presence of equimolar amounts of mercuric iodide,[11] silver tetrafluoroborate,[12] silver perchlorate, or silver 2,4,6-trinitrobenzenesulfonate.[13] These reagents all have limited scope for comparative kinetic studies, and indeed kinetic data in the literature are sparse. Second-order rate constants for the reactions of several dialkyl sulfides with methyl iodide have been reported by Pearson,[7] and a Hammett correlation for methylation of a series of substituted thioanisoles with dimethyl sulfate in benzyl alcohol at 45.2 °C has been published by Gosselck and Barth.[14]

We now wish to report a kinetic study of the methylation of variously substituted thioanisoles (**2**) and anilines (**5**) by 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (**1**),[15] a parallel set of systems (eq 1 and 2, respectively) selected to measure the relative nucleophilicities of bivalent sulfur vis-à-vis trivalent nitrogen of a comparable reference series.



(1)

(2)

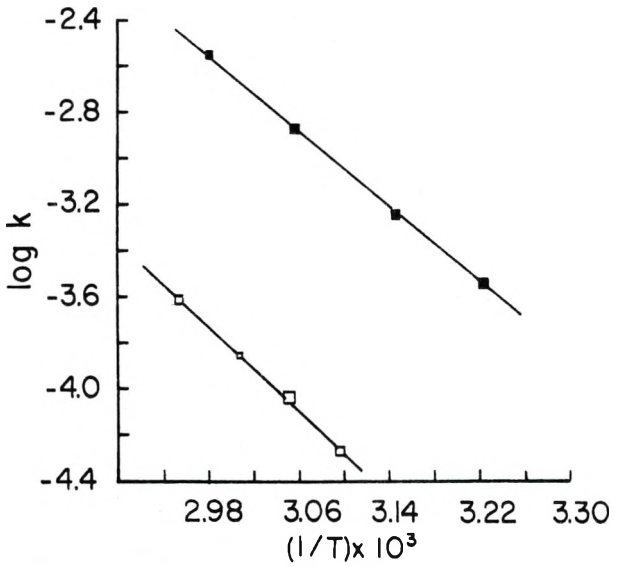


Figure 1. Representative Arrhenius plots for reaction of 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (1) with thioanisole (□) and with aniline (■). Second-order rate constants, k (M^{-1} s^{-1}), at various temperatures T (K), were determined in acetonitrile.

Table I. Second-Order Rate Constants for Reaction of 1 with Thioanisole at 65.3 ± 0.3 °C

[1], M	24.15×10^{-5}	38.19×10^{-5}	34.68×10^{-5}
[C_6H_5SMe], M	1.014	0.8685	0.5018
$10^4 k_2$, M^{-1} s^{-1} [a]	2.35 ± 0.03	2.43 ± 0.02	2.39 ± 0.04

[a] Average of two runs.

Results

A preliminary, preparative scale reaction of the dithiinium salt (1) with thioanisole (2, X = H) afforded a high yield (91%) of 2,5-diphenyl-1,4-dithiin (3) and dimethylphenylsulfonium tetrafluoroborate (4, X = H). Similarly, reaction of 1 with aniline in 16.5-fold excess showed the products to be 3 in 96% yield and *N*-methylaniline. VPC analysis of these last products showed only a minor trace of dimethylaniline, resulting from secondary alkylation.

Kinetic studies of the reactions of 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (1) with thioanisoles and anilines were carried out spectrophotometrically at various temperatures in acetonitrile under pseudo-first-order conditions with the nucleophile present in 10^2- to 10^3-fold excess. The derived second-order rate constants were independent of nucleophile concentration, as illustrated by representative data in Table I, and are completely summarized in the Experimental Section (Table VII). Representative Arrhenius plots for the two series are shown in Figure 1. Rate constants calculated at 330 K and activation thermodynamic parameters at 330 K are summarized in Table II. Hammett plots[16] (Figure 2) gave ρ values of −1.58 ± 0.05 (correlation coefficient 0.999) and −1.92 ± 0.06 (correlation coefficient 0.998) for the thioanisole and aniline series, respectively, at 330 K. The resulting array of data provided a basis for computation of second-order rate constants at selected common temperatures for comparison and correlation.

Discussion

It is well known that the Hammett ρ, defined in eq 3

$$\log \frac{k^X}{k^H} = \sigma_x \rho \tag{3}$$

provides a measure of the susceptibility of a reaction to variation of substitutents on a reactant.[16,17] According to Jaffe[16]

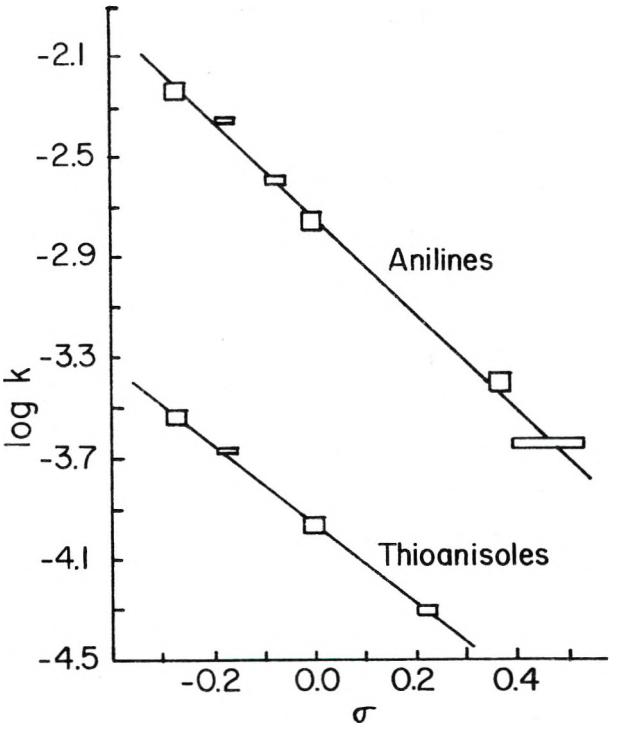


Figure 2. Hammett plots for the reactions of 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (1) with thioanisoles (ρ_S = −1.58 ± 0.05) and with anilines (ρ_N = −1.92 ± 0.06) at 330 K. Error blocks show standard deviations.

the three main factors which determine this susceptibility are (a) the reaction conditions, including solvent and temperature effects; (b) the transmission of electrical effects of substituent X to the reaction site; and (c) the susceptibility of the reaction to changes in electron density at the reaction site.

In the present study the reaction conditions were essentially identical. However, unlike the thioanisoles (2), the anilines (5) may be capable of hydrogen bonding with other aniline molecules and possibly with the solvent acetonitrile. The self-association of aniline has been studied by others[18] and does not appear to be significant at the concentrations used in this study. No data for the interaction of anilines with acetonitrile appear to be available. However, reactions of the dithiinium salt (1) with *N*-methylaniline and with *N,N*-dimethylaniline show second-order rate constants and activation thermodynamic parameters (cf. Table II) very similar to those of aniline itself suggesting that no significant H-bonding interactions occur in the system used.

Variations in the temperature dependence of ρ have been discussed by Wells[17] and others,[16,21] and are given, for the general case, by eq 4[17]

$$\rho = \frac{G_0}{T}\left(\frac{\partial \Delta G^{\ddagger}}{\partial \sigma}\right) \tag{4}$$

in which G_0 is a constant and the partial derivative $[\partial \Delta G^{\ddagger}/\partial \sigma = (\partial \Delta H^{\ddagger}/\partial \sigma) - T(\partial \Delta S^{\ddagger}/\partial \sigma)]$ is also temperature dependent, except for the few known cases where the reaction series are isoentropic. A comparison of the activation parameters in Table II shows that the activation processes for the thioanisole series are isoenthalpic ($\Delta H^{\ddagger}$ = 20.4 kcal/mol) within experimental error, hence ρ should be temperature invariant.[17,21] The aniline series is not so well defined, and a plot of activation enthalpies vs. entropies also shows no isokinetic relationship.[17,21] Values of ρ for both series were calculated at four temperatures in the range 25.0–80.0 °C and found to be constant [ρ_S = −1.58 ± 0.04 (thioanisoles) and ρ_N = −1.95 ± 0.05 (anilines)] within experimental error.

Table II. Activation Parameters and Rate Constants at 330 K[a]

Registry no.	Compd	$10^4 k$,[b] $M^{-1} s^{-1}$	$\Delta H^{\ddagger}$,[c] kcal/mol	$\Delta G^{\ddagger}$,[d] kcal/mol	$\Delta S^{\ddagger}$,[e] eu	σ[f,g]
123-09-1	*p*-Chlorothioanisole	0.488 ± 0.005	20.4 ± 0.2	25.89 ± 0.01	−16.6 ± 0.6	+0.227 ± 0.02
100-68-5	Thioanisole	1.07 ± 0.02	20.4 ± 0.9	25.38 ± 0.02	−15.1 ± 2.9	0
623-13-2	*p*-Methylthioanisole	2.15 ± 0.02	20.0 ± 0.2	24.92 ± 0.01	−14.9 ± 0.5	−0.17 ± 0.02
1879-16-9	*p*-Methoxythioanisole	2.87 ± 0.12	20.8 ± 0.7	24.73 ± 0.03	−11.9 ± 2.1	−0.268 ± 0.02
98-16-8	α,α,α-Trifluoro-*m*-toluidine	2.27 ± 0.06	18.6 ± 0.3	24.89 ± 0.02	−19.4 ± 0.9	+0.467 ± 0.071[g]
108-42-9	*m*-Chloroaniline	3.86 ± 0.06	19.1 ± 0.2	24.54 ± 0.01	−16.5 ± 0.6	+0.373 ± 0.02
62-53-3	Aniline	16.7 ± 0.3	17.8 ± 0.2	23.58 ± 0.02	−17.7 ± 0.7	0
108-44-1	*m*-Toluidine	24.9 ± 0.3	18.9 ± 0.1	23.32 ± 0.01	−13.3 ± 0.4	−0.069 ± 0.02
106-49-0	*p*-Toluidine	44.0 ± 0.9	18.5 ± 0.2	22.94 ± 0.01	−13.5 ± 0.7	−0.170 ± 0.02
104-94-9	*p*-Anisidine	57.9 ± 2.0	16.4 ± 0.4	22.76 ± 0.02	−19.6 ± 1.3	−0.268 ± 0.02
100-61-8	*N*-Methylaniline	31.9 ± 1.3	18.5 ± 0.7	23.15 ± 0.03	−14.4 ± 2.0	
121-69-7	*N*,*N*-Dimethylaniline	27.5 ± 1.3	17.4 ± 0.6	23.25 ± 0.03	−17.7 ± 1.8	

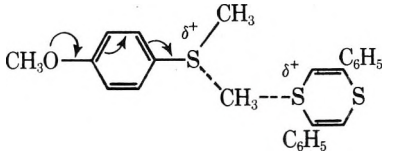
[a] All errors are standard deviations. [b] Calculated by Arrhenius equation: $\log k = (-E_{act}/2.3RT) + \log A$. [c] $\Delta H^{\ddagger} = E_{act} - RT$. [d] $k' = (kT/h)e^{-\Delta G^{\ddagger}/RT}$. [e] $\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta G^{\ddagger})/T$. [f] All values except CF_3 were taken from D. McDaniel and H. Brown, *J. Org. Chem.*, **23**, 420 (1958). [g] H. van Bekkum, P. Verkade, and B. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 815 (1959).

Table III. Second-Order Rate Constants ($M^{-1} s^{-1}$) and Differences in Activation Free Energy for Methylation of Thioanisoles (k_S^X) and Anilines (k_N^X) with I at 330 K

Substituent X	$10^4 k_S^X$	$10^4 k_N^X$	$\Delta\Delta G^{\ddagger}$, kcal/mol
p-MeO	2.87	57.9	1.97
p-Me	2.15	44.0	1.98
m-Me	(1.38)[a]	24.9	1.89
H	1.07	16.7	1.80
p-Cl	0.488	(6.13)[a]	1.65

[a] Interpolated data calculated from Hammett plots.

As mentioned in item b above, ρ is also determined by the balance of field, inductive, and resonance contributions[19] by which the electrical effect of substituent X is transmitted to the reaction site. In the present study only *p*-methoxythioanisole might have been expected to show unusual stabilization of the transition state via d-orbital conjugation of partially positive sulfur with the methoxy group, as suggested in the following approximation of the transition state structure



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(8). Since all of the substituents, including methoxy, correlated well with primary para (σ_p) and meta (σ_m) substituent constants, the ρ values for both the thioanisole and aniline series reflect parallel differences in their respective susceptibilities to substituent electrical effects.[20] Hence any special conjugation via d-orbital interaction is contraindicated.

Finally, the magnitude of ρ (cf. item c, above) is considered to be a measure of the magnitude of the developing charge at the reaction site.[21] In the present comparison there appears to be no qualitative difference between the behavior of the lone pair of electrons on sulfur or nitrogen, since the ρ values are quite similar. The slightly less negative value of ρ for the thioanisoles with respect to the anilines may simply reflect a more diffuse positive charge on the sulfur than that on the smaller nitrogen atom in their respective transition states.

Rate Correlations. Common Electrophile. A qualitative comparison of the specific rates of methylation of analogous thioanisoles and anilines shows that the ratios k_S^X/k_N^X (substituent X; S and N for the sulfur and nitrogen nucleophiles, respectively) range roughly from 0.02 to 0.04 at 25 °C, tending to increase at higher temperatures. These values are comparable with similar ratios obtained from Pearson's data[7] for reactions of methyl iodide with aliphatic sulfides and amines; e.g. $k_S/k_N = 0.034$ for tetrahydrothiopyran and piperidine at 25 °C.

On the basis of absolute reaction rate theory, for which the familiar equation $k' = (kT/h) \exp(-\Delta G^{\ddagger}/RT)$ applies, such rate ratios are given by

$$k_S^X/k_N^X = \exp(-\Delta\Delta G^{\ddagger}/RT) \quad (5)$$

where $\Delta\Delta G^{\ddagger}$ is the difference in activation free energy of two series members having given substituent X. This relationship suggested that if $\Delta\Delta G^{\ddagger}$ is approximately constant for all substituents X, a simple linear relationship of the form $k_S^X = mk_N^X + b$ may be applicable, in which the slope (m) should be approximated by the right-hand portion of eq 5 and b is a constant. Table III gives data at 330 K which clearly illustrate the variation in $\Delta\Delta G^{\ddagger}$. Despite this variation a least-squares regression line [$k_S^X = (0.0446 \pm 0.0013)k_N^X + (2.58 \pm 0.48)\ 10^{-5}$] showed an excellent correlation (coefficient $r = 0.998$), and a slope only slightly lower than expected from eq 5 [$\exp(-\Delta\Delta G^{\ddagger}/RT) = 0.059$] using a mean value of $\Delta\Delta G^{\ddagger}$ from Table III. However, similar data from other temperatures showed greater variations in $\Delta\Delta G^{\ddagger}$ and gave lines showing a distinct curvature, thus obviating broad correlation over the whole range of data. We therefore turned to the Hammett equation.

Since both the thioanisoles and anilines separately obey the Hammett relationship (eq 3) using the same primary σ_x values, elimination of σ_x between the two series equations leads to

$$\log k_S^X = \frac{\rho_S}{\rho_N} \log k_N^X + \left(\log k_S^H - \frac{\rho_S}{\rho_N} \log k_N^H\right) \quad (6)$$

in which the rate constants k^X cover all members of the series including $k^X = k^H$, and the intercept (in parentheses) is defined by the specific rates of the parent thioanisole and aniline. A plot of eq 6 is illustrated in Figure 3 for data at 56.8 °C, which falls within the range of the experimental rate determinations, and shows a correlation coefficient of greater than 0.999. A similar plot at 45.2 °C showed a correlation coefficient of 0.998. Although the slopes of both lines are slightly lower than expected from the ratio $\rho_S/\rho_N = -1.58/-1.95 = 0.81$ (calculated assuming both ρ values to be constant as discussed

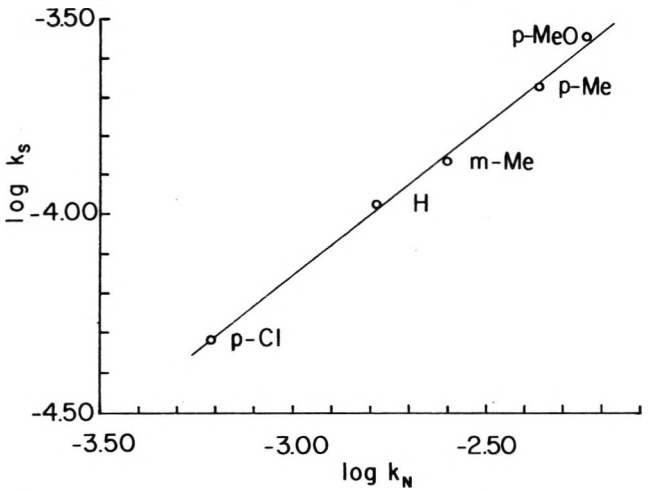


Figure 3. Logarithmic correlation of second-order rates of methylation of thioanisoles (k_S) and anilines (k_N) by 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (1) in MeCN at 330 K, following eq 6. The regression line: log k_S = (0.775 ± 0.019) log k_N − (1.826 ± 0.045) shows a correlation coefficient >0.999.

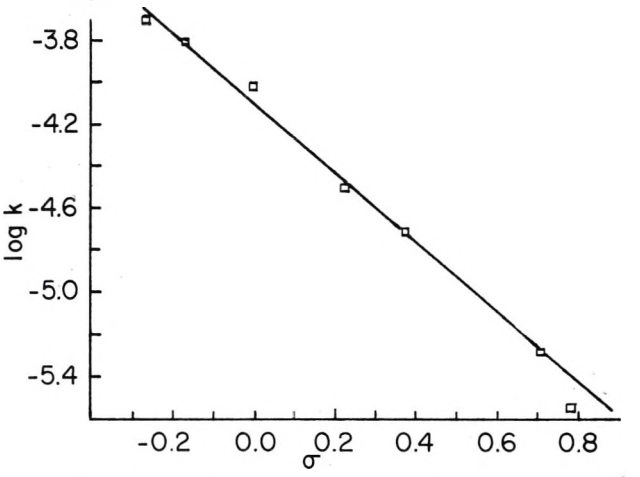


Figure 4. Hammett plot (ρ = −1.67 ± 0.06) for the reaction of dimethyl sulfate with thioanisoles in benzyl alcohol at 45.2 °C. Recalculated from the data of V. Gosselck and H. Barth, *Z. Naturforsch. B*, **16**, 280 (1961). Substituents (reading left to right) are *p*-MeO, *p*-Me, H, *p*-Cl, *m*-Cl, *m*-NO_2, *p*-NO_2.

earlier), the correlation based on eq 6 was quite satisfactory and found to be equally applicable at other temperatures.

It is of further interest that a parallel application of the Swain–Scott equation[22] to reactions of thioanisoles and anilines with a common electrophile such as compound 1 leads to eq 7, where k_0 is the rate constant of an arbitrary reference nucleophile and $n_S{}^X$ and $n_N{}^X$ are nucleophilic reactivity parameters for structurally comparable sets of thioanisoles and anilines, respectively.

$$\log k_S{}^X = \frac{n_S{}^X}{n_N{}^X} \log k_N{}^X + \left[\left(1 - \frac{n_S{}^X}{n_N{}^X}\right) \log k_0\right] \qquad (7)$$

The slope ($n_S{}^X/n_N{}^X$) of eq 7 represents the relative nucleophilicity of the thioanisoles with respect to the structurally comparable anilines based on a reference nucleophile defined only numerically by k_0 of the intercept term. Although this reference nucleophile is not chemically defined, it is apparent that, since the slopes of eq 6 and 7 are the same (i.e., $\rho_S/\rho_N = n_S{}^X/n_N{}^X$), the ratio of ρ values of the thioanisoles with respect to the analogous anilines represents a measure of the relative nucleophilicities of the two series.

Rate Correlations. Diverse Electrophiles. It was of additional interest to compare the rate behavior of a given series of nucleophiles, such as the thioanisoles or anilines, toward different electrophilic alkylating agents. Substituent effects for reactions 1 and 2 from the present study are compared with related series from the literature in Table IV. All values for literature reactions were recalculated using the σ_p and σ_m values of McDaniel and Brown.[23] Although ρ values are not strictly comparable, since ρ is solvent dependent,[16,24] the values for methylation of thioanisoles with dimethyl sulfate and with the dithiinium salt (1) are the same within experimental error.

Specific rate constants for reaction 1 and for the parallel alkylation of thioanisoles (2) with dimethyl sulfate[14] at 45.2 °C are summarized in Table V. A Hammett plot of the literature data is illustrated in Figure 4, which shows a significant deviation only for *p*-nitroanisole. Although Gosselck and Barth[14] made no comments about experimental errors, this deviation can probably be ascribed to enhanced resonance interaction involving simple p–π delocalization of the lone pair on sulfur with the nitro group as suggested by the canonical form (9) shown. In any case, since both σ and ρ are the same for both series, the Hammett relationship is simply log ($k_1/k_{Me_2SO_4}$) = constant, hence $k_1/k_{Me_2SO_4}$ = constant. Consequently, eq 5 based on transition state theory appeared applicable at constant temperature, with $\Delta\Delta G^{\ddagger}$ = constant. A direct plot of k_1 vs. $k_{Me_2SO_4}$ (Figure 5) showed a correlation coefficient of 0.992, a zero intercept within experimental error, and a constant reactivity ratio $k_1/k_{Me_2SO_4}$ = 0.43. Alternately, dimethyl sulfate is 2.3 times as reactive as the dithiinium salt (1) in the alkylation of a given thioanisole.

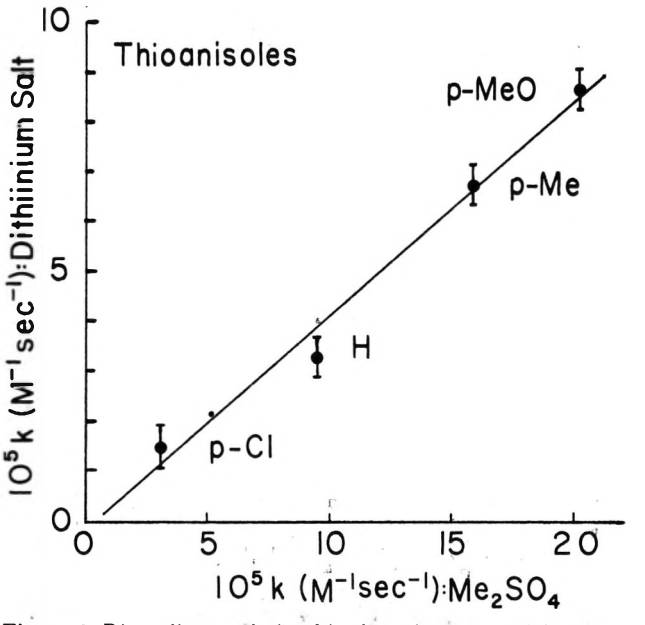
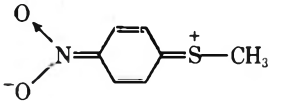


Figure 5. Direct linear relationship: k_1 = (0.43 ± 0.03) $k_{Me_2SO_4}$ − (0.156 ± 0.43) 10^{-5}, between the rates of methylation of thioanisoles by 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (1) in MeCN and by dimethyl sulfate in benzyl alcohol at 45.2 °C; correlation coefficient = 0.992; data from Table V.



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A similar comparison of the rates of alkylation of substituted anilines by the dithiinium salt (1) and by methyl iodide is illustrated in Figure 6, based on the data of Table VI. In order to make a comparison with literature data at 80 °C it was necessary in this case to extrapolate our kinetic data about 20

Table IV. Comparison of ρ Values for Methylation of Substituted Anilines and Thioanisoles

Methyl donor	Methyl acceptor	Solvent	Temp, °C	ρ[a]	Corr coeff	No. of points
CH_3I	$XC_6H_4NH_2$	$PhNO_2$	80	-2.14 ± 0.13[b]	0.993	6
Dithiinium salt (1)	$XC_6H_4NH_2$	CH_3CN	80	-1.83 ± 0.11[c]	0.993	6
Dithiinium salt (1)	$XC_6H_4SCH_3$	CH_3CN	80	-1.60 ± 0.03[c]	0.9997	4
$(CH_3)_2SO_4$	$XC_6H_4SCH_3$	$PhCH_2OH$	45.2	-1.67 ± 0.06[d]	0.998	6
Dithiinium salt (1)	$XC_6H_4SCH_3$	CH_3CN	45.2	-1.57 ± 0.07[c]	0.998	4

[a] Error is standard error. [b] Calculated from data of P. Randhakrishnamurti and L. Panigrahi, *J. Indian Chem. Soc.*, **46**, 567 (1969). [c] This work. [d] V. Gosselck and H. Barth, *Z. Naturforsch. B*, **16**, 280 (1961). Does not include p-NO_2. These authors incorrectly reported ρ as −1.14.

Table V. Comparison of Methylation of Substituted Thioanisoles with Dimethyl Sulfate and 1-Methyl-2,5-diphenyl-1,4-dithiinium Tetrafluoroborate (1) at 45.2 °C

Substituent	Dimethyl sulfate[a] $10^5 k$, l./mol·s	1,[b,c] $10^5 k$, l./mol·s	σ[d]
p-NO_2	0.283		+0.778
m-NO_2	0.520		+0.710
m-Cl	1.93		+0.373
p-Cl	3.10	1.51	+0.227
H	9.50	3.32	0
p-CH_3	15.9	6.77	−0.170
p-CH_3O	20.3	8.66	−0.238

[a] V. Gosselck and H. Barth, *Z. Naturforsch. B*, **16**, 280 (1961). Solvent: benzyl alcohol. [b] This work. Solvent: acetonitrile. [c] Computed from Arrhenius equation. [d] All values from D. McDaniel and H. Brown, *J. Org. Chem.*, **23**, 420 (1958).

Table VI. Comparison of Methylation of Substituted Anilines with Methyl Iodide and 1-Methyl-2,5-diphenyl-1,4-dithiinium Tetrafluoroborate (1) at 80 °C

Substituent	Methyl iodide[a] $10^4 k$, l./mol·s	1,[b,c] $10^4 k$, l./mol·s	σ[d]
m-CF_3		15.4	+0.467 ± 0.071[e]
m-Br	1.94		+0.391 ± 0.02
m-Cl	1.57	27.8	+0.373 ± 0.02
p-Cl	3.26		+0.227 ± 0.02
H	9.22	106	0
m-CH_3	16.0	176	−0.069 ± 0.02
p-CH_3	28.0	298	−0.170 ± 0.02
p-CH_3O		318	−0.268 ± 0.02

[a] P. Randhakrishnamurti and G. Panigrahi, *J. Indian Chem. Soc.*, **46**, 567 (1969). Solvent: nitrobenzene. [b] This work. Solvent: acetonitrile. [c] Computed by Arrhenius equation. [d] All values except m-CF_3 from D. McDaniel and H. Brown, *J. Org. Chem.*, **23**, 420 (1958). [e] H. van Bekkum, P. Verkade, and B. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 815 (1959).

°C beyond the range of experimental determinations by using individual Arrhenius equations. Furthermore, since only four substituents among the two sets were directly comparable without still further, and inappropriate, extrapolation based on the Hammett equation, the high correlation coefficient (0.999) probably exaggerates the agreement. Nevertheless, except for the low intercept, which cannot be precisely explained, the rate constants for alkylation of anilines with 1 and with methyl iodide again appear to be a simple linear function. Overall, the dithiinium salt (1) is about ten times as reactive as methyl iodide toward the anilines.

Finally, it is noteworthy that, although the activation energy

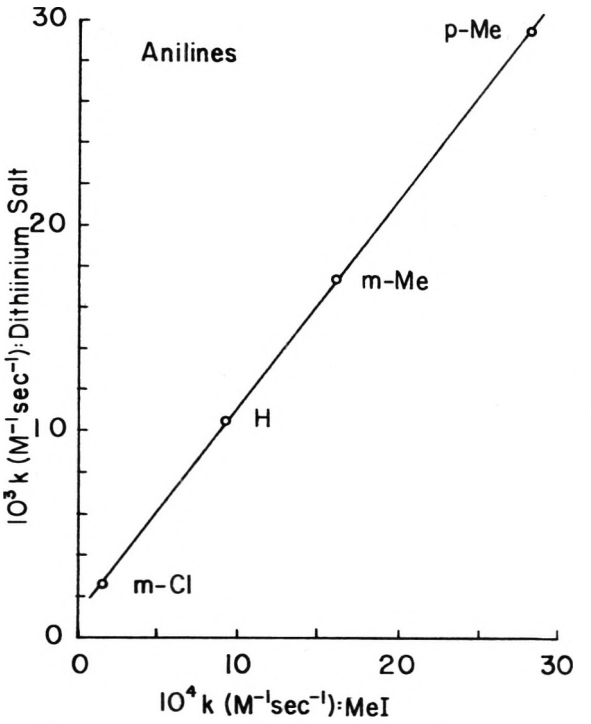

Figure 6. Linear relationship: $k_1 = (10.23 \pm 0.02)\, k_{MeI} + (11.9 \pm 0.3)\ 10^{-4}$; corr coeff >0.999, between the rates of methylation of anilines by 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (1) in MeCN and by methyl iodide in nitrobenzene at 80 °C; data from Table VI.

for the reaction of aniline with methyl iodide (E_{act} = 8.77 kcal/mol) is much smaller than for similar alkylation with the S-methyl dithiinium salt (1) (E_{act} = 18.4 kcal/mol), the activation entropy at 80 °C is vastly more negative for the methyl iodide ($\Delta S^{\ddagger} = -49.9$ eu) reaction than for the reaction of the sulfonium alkylating agent (1: $\Delta S^{\ddagger} = -17.8$ eu). This entropy difference may reflect a greater degree of bonding between the nucleophilic center and the methyl group in methyl iodide, as also implied by the more negative ρ values (cf. Table IV), or alternately may indicate less constraint in the approach route of the nucleophile attacking the carbon of the methylsulfonium system (1).[25]

Experimental Section

Apparatus. Ultraviolet spectra and kinetic data were obtained with a Perkin-Elmer 402 uv–visible spectrophotometer fitted with a cast iron cell block. Constant temperature (±0.03 °C) was maintained by circulating water from a Forma-Temp Jr. constant temperature bath and circulator through a jacketed 1-cm sample cell and the cell block. Reaction temperatures were read (±0.3 °C) from a calibrated thermometer in the cell block. NMR spectra were recorded on a Hitachi Perkin-Elmer R-20A spectrometer. VPC analyses were carried out with a Nester-Faust Anakro IA chromatograph fitted with a silicone SE-30 column. Melting points were determined in capillary tubes using a calibrated Mel-Temp apparatus.

Table VII. Effect of Temperature on the Rate of Methylation of Nucleophiles by 1

Temp, ±0.3 °C	$10^4 k_2$, l./mol·s	Temp, ±0.3 °C	$10^4 k_2$, l./mol·s
Aniline		*N*-Methylaniline	
37.1	2.85 ± 0.06	40.2	6.70 ± 0.13
44.8	5.62 ± 0.10	48.6	15.8 ± 0.7
54.0	13.0 ± 0.4	53.7	23.0 ± 0.8
62.2	26.5 ± 0.5	59.0	39.1 ± 3.5
m-Chloroaniline		*N,N*-Dimethylaniline	
41.1	0.855 ± 0.018	36.8	4.63 ± 0.17
48.9	1.85 ± 0.07	40.0	6.03 ± 0.04
56.7	3.73 ± 0.11	48.6	14.5 ± 0.2
63.4	7.04 ± 0.14	56.6	26.0 ± 0.2
p-Toluidine		Thioanisole	
31.5	3.85 ± 0.02	50.0	0.535 ± 0.014
40.3	9.37 ± 0.02	54.6	0.890 ± 0.054
49.3	22.9 ± 0.6	59.6	1.37 ± 0.06
56.9	43.3 ± 0.6	65.3	2.40 ± 0.05
p-Anisidine		*p*-Methylthioanisole	
39.0	12.7 ± 0.6	48.7	0.964 ± 0.025
44.7	22.5 ± 0.4	54.6	1.72 ± 0.04
47.9	28.2 ± 1.1	60.5	3.07 ± 0.03
56.9	56.3 ± 1.0	67.0	5.45 ± 0.09
59.5	72.0 ± 1.0		
α,α,α-Trifluoro-*m*-toluidine		*p*-Chlorothioanisole	
		54.5	0.389 ± 0.010
43.8	0.693 ± 0.023	59.6	0.638 ± 0.010
49.8	1.14 ± 0.04	64.3	0.976 ± 0.019
56.7	2.21 ± 0.06	69.9	1.67 ± 0.03
63.4	4.02 ± 0.05		
65.3	4.71 ± 0.06	*p*-Methoxythioanisole	
m-Toluidine		49.3	1.28 ± 0.02
		54.8	2.46 ± 0.05
37.4	3.81 ± 0.04	60.1	4.00 ± 0.03
44.8	8.01 ± 0.13	67.0	7.44 ± 0.23
51.4	15.3 ± 0.5		
59.2	30.4 ± 0.5		

Materials. 1-Methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (**1**) was prepared by the method of Young and Lazarus.[15] The amines, which were commercially available, were purified either by distillation under reduced pressure or by recrystallization followed by sublimation. All of the sulfides except *p*-methoxythioanisole were commercial products purified by distillation under reduced pressure. *p*-Methoxythioanisole was prepared according to the procedure of Bordwell and Pitt[26] and was distilled under reduced pressure to give pure product with a boiling point in agreement with literature values. Acetonitrile (Fisher Certified) was distilled three times from phosphorus pentoxide.

Acetonitrile solutions of the dithiinium salt (**1**) were stable indefinitely at room temperature and for at least 24 h at 66 °C, which represents the upper limit of temperature for these studies. Solutions of 2,5-diphenyl-1,4-dithiin (**3**) at 66 °C likewise showed no ultraviolet absorbance change for at least the several hours necessary to monitor the aniline reactions. Literature reports of failure of amines to react with acetonitrile[27,28] were confirmed by observing no change in the NMR spectrum of a 1.5 M solution of aniline in acetonitrile at 63 °C overnight. Therefore, competing reactions under the conditions used to study the methylation of anilines are insignificant. In contrast, solutions of the dithiin (**3**) and thioanisole showed a steady increase in absorbance over a period of hours at 66 °C which would complicate the study of the slower reacting thioanisoles. Apparently this increase was due to oxidation, since careful flushing of the solutions for the thioanisole kinetics with dry nitrogen eliminated the problem.

Identification of Products. Reaction of 1 with Aniline. Six grams (0.0162 mol) of 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (**1**) and 25.0 g (0.268 mol) of aniline were heated at 78 °C for 3 h. The solution was cooled and the precipitated 2,5-diphenyl-1,4-dithiin (**3**) was removed by filtration. After it was concentrated on a rotary evaporator, an approximately 0.1 M solution of HCl was added to the filtrate to precipitate the remaining 2,5-diphenyl-1,4-dithiin (**3**), which was combined with the previous material to give a total yield of 4.15 g (96%). Ammonium hydroxide was then added to separate an amine layer which was extracted into ether and distilled from calcium hydride. VPC analysis showed the mixture to be aniline and *N*-methylaniline with only a trace of *N,N*-dimethylaniline.

Reaction of 1 with Thioanisole. A solution of 0.50 g (0.0014 mol) of 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (**1**) and 0.25 g (0.002 mol) of thioanisole in 1 ml of acetonitrile was maintained at 65 °C for 18 h. Concentration of the solution led to precipitation of 0.30 g of crude 2,5-diphenyl-1,4-dithiin (**3**). Addition of ether precipitated 0.24 g (79%) of a white solid with mp 131–132.5 °C. Evaporation of the filtrate to near dryness allowed the collection of another 0.03 g of **3** to give a total crude yield of 0.33 g (91%), which after one recrystallization from absolute ethanol weighed 0.20 g (55%) with mp 114–116 °C (lit.[29] mp 115–117 °C). Recrystallization of the hygroscopic white solid from acetonitrile–ether and drying in vacuo with phosphorus pentoxide gave analytically pure dimethylphenylsulfonium tetrafluoroborate with mp 132.5–133.5 °C; NMR (CD_3CN) δ 3.17 (s, 6, CH_3's), 7.8 ppm (m, 5, ArH).

Anal. Calcd for $C_8H_{11}BF_4S$: C, 42.51; H, 4.91; S, 14.18. Found: C, 42.59; H, 4.95; S, 14.11.

Kinetic Measurements. The progress of the reactions described herein was followed by observing the decrease in ultraviolet absorbance at 340 nm. Beer's law plots of the 2,5-diphenyl-1,4-dithiin (**3**) and 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (**1**) were linear and passed through the origin. A least-squares computer procedure gave molar extinction coefficients (ε) of 1.05×10^3 and 4.72×10^3 for the dithiin (**3**) and the dithiinium salt (**1**), respectively. Since the reactions were run with an initial dithiinium salt concentration ($S_{t=0}$) of about 20×10^{-5} M and a nucleophile concentration (N) of about 0.01–1.0 M, the integrated rate equation is given by eq 8 fol-

lowing, where S_t = molar concentration of dithiinium salt (1) and D_t = molar concentration of dithiin (3) at time t.

$$\ln\frac{S_{t_1}}{S_{t_2}} = kN(t_2 - t_1) \quad (8)$$

Since

$$A_t = \epsilon_S S_t + \epsilon_D D_t \text{ and } D_t = S_{t=0} - S_t,$$

$$A_t = S_t(\epsilon_S - \epsilon_D) + \epsilon_D S_{t=0} \text{ or } S_t = \frac{(A_t - \epsilon_D S_{t=0})}{\epsilon_S - \epsilon_D}$$

Substitution of this latter equation for S_t into eq 8 gives the final rate equation 9.

$$\ln\frac{A_{t_1} - \epsilon_D S_{t=0}}{A_{t_2} - \epsilon_D S_{t=0}} = kN(t_2 - t_1) \quad (9)$$

Pseudo-first-order plots of ln $(A_t - \epsilon_D S_{t=0})$ vs. time were linear to 2–4 half-lives and both the aniline and thioanisole reactions were found to go essentially to completion. Any absorbance due to the nucleophiles was cancelled by placing in the reference beam a solution of nucleophile of exactly the same concentration as that in the reaction solution. All kinetic determinations were made in triplicate with agreement usually better than ±5%.

Stock solutions of the dithiinium salt (1) and the nucleophile were prepared in the bath. The reaction was started by pipetting a known volume of the dithiinium salt solution into a 10-ml volumetric flask and diluting to the mark with the stock nucleophile solution. In the case of the thioanisole series reactions, dry nitrogen was slowly bubbled through the stock solutions cooled in an ice bath for ca. 20 min and through the reaction solution for about 10 min before placing it in the sample cell. The nucleophile concentrations were typically 0.01–0.20 M for the aniline series reactions and 0.2–1.0 M for the thioanisole series reactions. In the case of the aniline series the five-fold ordinate expansion system of the spectrophotometer was used and the calculated rate constant was usually based on the first 15–30% of the reaction. The normal ordinate plot was used for the thioanisole series and the rate constants were based on approximately the first 75% of the reaction.

Derived rate constants are summarized in Table VII, with errors given as standard deviations. The temperature error (±0.3 °C) represents the outer limits of control as measured at the cell block. A time-averaged standard deviation of temperature in the reaction cuvette could not be determined directly, but was necessarily less than ±0.3 °C.

Registry No.—1, 17250-79-2; *p*-chloroaniline, 106-47-8; *m*-methylthioanisole, 4886-77-5; dimethylphenylsulfonium tetrafluoroborate, 33613-52-4.

References and Notes

(1) Based in part on the Ph.D. Dissertation of Alan R. Oyler, Lehigh University, 1973.
(2) National Science Foundation Trainee, 1970–1973.
(3) D. M. Greenberg, *Adv. Enzymol.*, **25**, 395 (1963).
(4) S. K. Shapiro and F. Schlenk, Ed., "Transmethylation and Methionine Biosynthesis", University of Chicago Press, Chicago, Ill., 1965.
(5) L. Jaenicke and H. Rudiger, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **30**, 160 (1971).
(6) V. Zappia, C. Zydek-Cwick, and F. Schlenk, *J. Biol. Chem.*, **244**, 4499 (1969).
(7) R. G. Pearson, H. Sobel, and J. Songstad, *J. Am. Chem. Soc.*, **90** 319 (1968).
(8) G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, **89**, 3607 (1967).
(9) J. K. Coward and W. D. Sweet, *J. Org. Chem.*, **36**, 2337 (1971).
(10) Houben-Weyl, "Methoden der Organischen Chemie", Vol. 9, Georg Thieme Verlag, Stuttgart, 1955.
(11) J. van der Veen, *Recl. Trav. Chim. Pays-Bas*, **84**, 540 (1965).
(12) V. Franzen, H. Schmidt, and C. Mertz, *Chem. Ber.*, **94**, 2942 (1961).
(13) D. J. Petit and G. K. Helmkamp, *J. Org. Chem.*, 29, 2702 (1964).
(14) V. Gosselck and H. Barth, *Z. Naturforsch. B*, **16**, 280 (1961).
(15) T. E. Young and R. A. Lazarus, *J. Org. Chem.*, **33**, 3770 (1968).
(16) H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).
(17) P. Wells, *Chem. Rev.*, **63**, 171 (1963); P. Wells, "Linear Free Energy Relationships", Academic Press, New York, N.Y., 1968, pp 20–22.
(18) J. Lady and K. Whetsel, *J. Phys. Chem.*, **68**, 1001 (1964).
(19) M. Dewar and P. Grisdale, *J. Am. Chem. Soc.*, **84**, 3539, 3548 (1962).
(20) L. P. Hammett, "Physical Organic Chemistry", 2d ed, McGraw-Hill, New York, N.Y., 1970, p 357.
(21) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963, Chapter 7, p 177.
(22) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).
(23) D. McDaniel and H. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(24) Y. Kondo, T. Matsue, and N. Tokura, *Bull. Chem. Soc. Jpn.*, **42**, 1037 (1969).
(25) Reference 21, p 68.
(26) F. Bordwell and B. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).
(27) L. Exner, M. Hurwitz, and P. Denneville, *J. Am. Chem. Soc.*, **77**, 1103 (1955).
(28) G. Reynolds, W. Humphlett, F. Swamer, and C. Hauser, *J. Org. Chem.*, **16**, 165 (1951).
(29) R. H. Barker and C. Barkenbus, *J. Am. Chem. Soc.*, **58**, 262 (1936).

Reactions of Acyl Thiochlorosulfites

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p-Chlorobenzoyl thiochlorosulfite (**1b**) reacted with thiophenols or potassium xanthates to give acyl aryl dithiosulfites (**3**) or acylalkoxythiocarbonyl dithiosulfites (**4**). The reaction of 1 mol of **1b** with 1.5 mol of aniline gave bis-*p*-chlorobenzoyl dithiosulfite (**2b**) and *N*-sulfinylaniline, whereas 1 mol of **1b** with 2 mol of aniline afforded *p*-chlorobenzanilide. Carboxylic acids with **1b** in the presence of triethylamine gave carboxylic anhydrides and **2b**. Reaction of **1** with potassium thiocyanate gave acyl isothiocyanates.

Previously, one of the authors has reported the preparation of diacyl dithiosulfites RCOSS(O)SCOR′ (**2**) and acyl thiochlorosulfites RCOSS(O)Cl (**1**) by the reaction of thiocarboxylic acids and thionyl chloride.[1] Although chlorosulfites ROS(O)Cl are readily prepared from thionyl chloride and alcohols, thiochlorosulfites RSS(O)Cl have not been isolated and their formation has been only postulated as intermediates in the reaction of thionyl chloride and mercaptans.[2] Accordingly, it appeared of interest to investigate the reactions of **1** with various nucleophilic reagents. Aroyl thiochlorosulfites (**1**, R = Ar) are more stable than acyl thiochlorosulfites (**1**, R = alkyl) and some of the former could be isolated as crystalline solids. Reactions were then examined with *p*-chlorobenzoyl thiochlorosulfite (**1b**, R = *p*-ClC_6H_4) which was especially stable and convenient to handle.

Results and Discussion

Thiobenzoic acid or *p*-chlorothiobenzoic acid was allowed to react with thionyl chloride at low temperature to give benzoyl thiochlorosulfite[1] (**1a**) or *p*-chlorobenzoyl thiochlorosulfite (**1b**) in 60–80% yield (eq 1). Acyl thiochlorosulfites were readily hydrolyzed to give diacyl dithiosulfites[1] (**2**) in

Table I[a]

RCSSSR′
‖ ↓
O O

Registry no.	Compd	R	R′	Mp, °C	Yield, %	Ir (KBr), cm^{-1} $\nu_{C=O}$	Ir (KBr), cm^{-1} $\nu_{S\rightarrow O}$
59318-18-2	**3a**	C_6H_5	p-ClC_6H_4	99–102	47	1675	1130
59318-19-3	**3b**	p-ClC_6H_4	C_6H_5	83–87	36	1675	1120
59318-20-6	**3c**	p-ClC_6H_4	p-ClC_6H_4	99–103	64	1675	1130
59318-21-7	**3d**	p-ClC_6H_4	p-$CH_3C_6H_4$	94–100	38	1675	1130

[a] Satisfactory analyses (±0.4% for C, H, and S) were reported for all compounds in table. Ed.

Table II[a]

RCSSSCOR′
‖ ↓ ‖
O O S

Registry no.	Compd	R	R′	Mp, °C	Yield, %	Ir (KBr), cm^{-1} $\nu_{C=O}$	Ir (KBr), cm^{-1} $\nu_{S\rightarrow O}$
59318-22-8	**4a**	p-ClC_6H_4	C_2H_5	89–90	25	1675	1150
59318-23-9	**4b**	p-ClC_6H_4	i-C_3H_7	86–88	50	1660	1150
59318-34-0	**4c**	p-ClC_6H_4	n-C_4H_9	60–61	66	1680	1150

[a] See footnote *a*, Table I.

quantitative yield and no other products were obtained. The result indicates that **1** is initially hydrolyzed to thiocarboxylic acids, which react rapidly with **1**, yielding the final products **2** (eq 2, 3).

$$\underset{\underset{\|}{O}}{RCSH} + SOCl_2 \longrightarrow \underset{\underset{O\ O}{\|\ \downarrow}}{RCSSCl} + HCl \qquad (1)$$

1

$$\mathbf{1} \xrightarrow{H_2O} \underset{\underset{O}{\|}}{RCSH} + SO_2 + HCl \qquad (2)$$

$$\underset{\underset{O}{\|}}{RCSH} + \mathbf{1} \longrightarrow \underset{\underset{O\ O\ O}{\|\ \downarrow\ \|}}{RCSSSCR} + HCl \qquad (3)$$

2

Treatment of **1** with thiophenols gave new mixed anhydrides, acyl aryl dithiosulfites (**3**), in the yields of 36–64% (eq 4). The results are summarized in Table I. By the decompo-

$$\mathbf{1} \xrightarrow{R'SH} \underset{\underset{O\ O}{\|\ \downarrow}}{RCSSSR'} \xrightarrow[-SO_2]{\Delta} \underset{\underset{O}{\|}}{RCSSR'} + R'SSR' + \underset{\underset{O\ O}{\|\ \|}}{RCOCR} \qquad (4)$$

3

sition of **3c** at the melting point p-chlorobenzoyl p-chlorophenyl disulfide, bis-p-chlorophenyl disulfide, and a small amount of p-chlorobenzoic anhydride were formed with evolution of sulfur dioxide.

Potassium xanthates reacted with **1b** to give acylalkoxythiocarbonyl dithiosulfites (**4**) in 25–66% yields (eq 5). These

$$\mathbf{1b} \xrightarrow{\underset{\underset{S}{\|}}{KSCOR'}} \underset{\underset{O\ O\ S}{\|\ \downarrow\ \|}}{RCSSSCOR'} \xrightarrow[-SO_2]{\Delta} \underset{\underset{O\quad O}{\|\quad \|}}{RCSSSCR} + \underset{\underset{O\ O}{\|\ \|}}{RCOCR} + \underset{\underset{S}{\|}}{(R'OCS)_2} \qquad (5)$$

4

new compounds have also interesting mixed anhydride structure. The results are summarized in Table II. By the decomposition of **4a** at the melting point bis-p-chlorobenzoyl trisulfide, p-chlorobenzoic anhydride, and bisethoxythiocarbonyl disulfide were formed with evolution of sulfur dioxide.

Dialkylammonium dialkyldithiocarbamates reacted with **1b** at −30 °C to give an oily product. The ir of the oil ($\nu_{C=O}$ 1690 cm^{-1}, $\nu_{S\rightarrow O}$ 1150 cm^{-1}) appeared in a different region from those of **1b** and the spectra of the fingerprint region resembled closely that of dithiocarbamates. So the product was assumed to be acylthiocarbamoyl dithiosulfites (**5**). This product was unstable and gradually decomposed at room temperature to give N-dialkyl-p-chlorobenzamides and sulfur with evolution of sulfur dioxide (eq 6).

$$\mathbf{1b} \xrightarrow{\underset{\underset{S}{\|}}{R_2'NH_2SCNR_2'}} \left[\underset{\underset{O\ O\ S}{\|\ \downarrow\ \|}}{RCSSSCNR_2'}\right] \xrightarrow[-SO_2]{} \underset{\underset{O}{\|}}{RCNR_2'} + S \qquad (6)$$

5

In the reaction of **1b** with aniline the molar ratio of the reagents markedly affected the variety of the products. The reaction of 1 mol of **1b** with 1.5 mol of aniline at low temperature gave bis-p-chlorobenzoyl dithiosulfite (**2b**), N-sulfinylaniline, and aniline hydrochloride, whereas 1 mol of **1b** with 2 mol of aniline afforded p-chlorobenzanilide, sulfur, and aniline hydrochloride. In each case, products were obtained in almost quantitative yields based on the following equations.

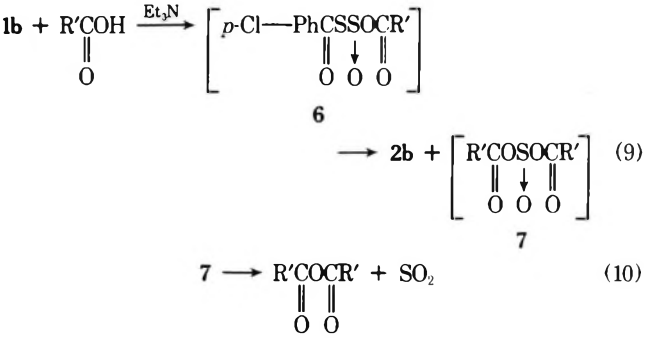
$$\mathbf{1b} + 1.5PhNH_2 \longrightarrow \tfrac{1}{2}\mathbf{2b} + \tfrac{1}{2}PhNSO + PhNH_3Cl \qquad (7)$$

$$\mathbf{1b} + 2PhNH_2 \longrightarrow p\text{-}Cl\text{—}\underset{\underset{OH}{|}}{PhCNPh} + PhNH_3Cl + 1\tfrac{1}{2}S + \tfrac{1}{2}SO_2 \qquad (8)$$

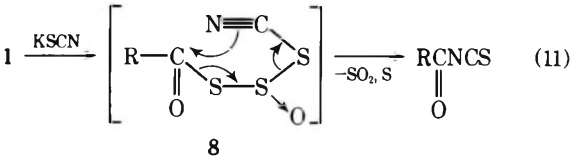
The reaction of **1b** with 2 mol of diethylamine gave N-diethyl-p-chlorobenzamide, sulfur, and diethylamine hydrochloride with evolution of sulfur dioxide. Triethylamine promoted the decomposition of **1b** at low temperature to give p-chlorobenzoyl chloride.

The reaction of **1b** with carboxylic acids in the presence of triethylamine gave carboxylic anhydrides, bis-p-chlorobenzoyl dithiosulfite (**2b**), and triethylamine hydrochloride with evolution of sulfur dioxide. It seems reasonable to assume that

diacyl monothiosulfites (**6**) are initially formed (eq 9) and then disproportionate to give **2b** and diacyl sulfites (**7**) which decompose subsequently to carboxylic anhydrides and sulfur dioxide (eq 9, 10).



The reaction of **1** with potassium thiocyanate afforded acyl isothiocyanates. The product was assumed to be formed by intramolecular rearrangement of **8** (eq 11).



Reaction of **1** with alcohol at low temperature did not proceed at all. At room temperature decomposition of **1** took place preferentially prior to the reaction with alcohol.

Experimental Section

Infrared spectra were measured with a Hitachi EPI-G2 spectrometer. The NMR spectra were determined on $CDCl_3$ or CCl_4 solutions with a Varian A-60 spectrometer. *p*-Chlorothiobenzoic acid was prepared as previously described.[1] All other reagents were obtained commercially.

Benzoyl Thiochlorosulfite (1a) and *p*-Chlorobenzoyl Thiochlorosulfite (1b). Preparation of **1a** from thionyl chloride and thiobenzoic acid has been reported in the previous paper.[1] Similarly **1b** was obtained: yield 82%; mp 71–74 °C; ir $\nu_{C=O}$ 1665, $\nu_{S\rightarrow O}$ 1200 cm^{-1} (CCl_4). Anal. Calcd for $C_7H_4Cl_2O_2S_2$: C, 32.95; H, 1.58; S, 25.13. Found: C, 33.16; H, 1.81; S, 25.02.

Hydrolysis of 1. A solution of 8.7 g (0.034 mol) of **1b** in 40 ml of THF was added dropwise to a stirred 200 ml of water at room temperature during 1 h. After the addition was completed, the white precipitated material was collected by filtration and dried to yield 6.4 g (96%) of bis-*p*-chlorobenzoyl dithiosulfite (**2b**), mp 130 °C.[1] In a similar way **1a** gave dibenzoyl dithiosulfite (**2a**), mp 108 °C,[1] yield 95%.

Reaction of 1 with Thiophenols. A solution of 0.04 mol of thiophenol in 20 ml of ether was added dropwise to a solution of 0.04 mol of **1** in 40 ml of ether at −40 °C during 1 h. Stirring was continued for an additional 2 h and then the temperature of the mixture was allowed to rise to −10 °C. The precipitated material was collected and recrystallized from petroleum ether to yield **3a–d.**

Thermal Decomposition of 3. *p*-Chlorobenzoyl *p*-chlorophenyl dithiosulfite (**3c**, 0.5 g) was heated at 100–110 °C for 1 h under nitrogen atmosphere. After standing at room temperature the mass turned to a mixture of yellow liquid and white solid. Recrystallization of the mixture from *n*-hexane gave 0.05 g of *p*-chlorobenzoic anhydride, mp 192–193 °C (lit. 194 °C). The filtrate was evaporated and the residue was chromatographed on silica gel using CCl_4 as eluent to give 0.1 g of bis-*p*-chlorophenyl disulfide, mp 71 °C (lit. 70–71 °C), and 0.1 g of *p*-chlorobenzoyl *p*-chlorophenyl disulfide, mp 62–65 °C. Anal. Calcd for $C_{13}H_8Cl_2OS_2$: C, 49.53; H, 3.19. Found: C, 49.82; H, 2.96.

Reaction of 1b with Potassium Xanthates. To a solution of 0.03 mol of **1b** in 80 ml of ether, 0.03 mol of powdered potassium xanthate was added little by little with stirring at −30 °C. Stirring was continued for an additional 2 h and then the temperature of the mixture was allowed to rise to −10 °C. Precipitated material was filtered and the filtrate was evaporated. The residual solid was combined with the precipitate and recrystallized from petroleum ether to yield **4a–c.** Since the product was contaminated with **2b** as persistent impurity, recrystallization was required for several times. NMR ($CDCl_3$) of **4a**, δ 1.50 (t, 3, CH_3), 4.79 (q, 2, CH_2), 7.65 (m, 4, phenyl); **4b**, 1.55 (d, 6, CH_3), 5.83 (m, 1, CH), 7.65 (m, 4, phenyl); **4c**, 0.76–2.16 (m, 7, $CH_2CH_2CH_3$), 4.71 (t, 2, $-OCH_2$), 7.63 (m, 4, phenyl).

Thermal Decomposition of 4. *p*-Chlorobenzoyl ethoxythiocarbonyl dithiosulfite (**4a**, 3.2 g) was heated at 90–100 °C for 1 h under nitrogen atmosphere. After standing at room temperature, the mass turned to a mixture of yellow liquid and solid. The mixture was filtered and washed with petroleum ether. Recrystallization of the solid with benzene and *n*-hexane gave 0.5 g of *p*-chlorobenzoic anhydride, mp 193 °C (lit. 194 °C), and 0.7 g of bis-*p*-chlorobenzoyl trisulfide, mp 125–126 °C. Anal. Calcd for $C_{14}H_8Cl_2O_2S_3$: C, 44.80; H, 2.15; S, 25.63. Found: C, 44.92; H, 2.12; S, 25.50. The filtrate was evaporated to give 1.2 g of yellow oil. Distillation of the oil gave 0.5 g of bisethoxythiocarbonyl disulfide: bp 125 °C (0.5 mm) [lit.[3] bp 107–109 °C (0.05 mm)]; ir[4] 1245 (s), 1150 (w), 1110 (m), and 1020 cm^{-1} (s).

Reaction of 1b with Dialkylammonium Dialkyldithiocarbamates. A solution of 8.2 g (0.032 mol) of **1b** in 30 ml of THF was added to a suspension of 5.3 g (0.032 mol) of dimethylammonium dimethyldithiocarbamate in 40 ml of THF at −30 °C during 2 h. Stirring was continued for an additional 3 h and then the temperature of the mixture was allowed to rise to room temperature. Precipitated dimethylammonium chloride was filtered and the filtrate was evaporated under reduced pressure giving **5a** as a light yellow oil. Distillation of the oil gave *N*-dimethyl-*p*-chlorobenzamide: yield 4.1 g (70%); bp 128–130 °C (1.2 mm); mp 57 °C (lit.[5] 59–60 °C); ir $\nu_{C=O}$ 1635 cm^{-1}. Diethylammonium diethyldithiocarbamate reacted similarly with **1b** to give *N*-diethyl-*p*-chlorobenzamide: yield 52%; bp 125 °C (0.5 mm) [lit.[6] 115 °C (0.2 mm)]; ir $\nu_{C=O}$ 1630 cm^{-1}.

Reaction of 1b with a 1.5 Molar Quantity of Aniline. A solution of 9.0 g (0.035 mol) of **1b** in 50 ml of ether was added to a stirred solution of 4.9 g (0.053 mol) of aniline in 20 ml of ether at −30 °C during 1.5 h. After the addition was completed the reaction mixture was stirred at the same temperature for 1 h. Precipitated material was filtered and washed with 20 ml of petroleum ether. The filtrate was evaporated to give *N*-sulfinylaniline which was identified by infrared spectrum.[7] The amount of *N*-sulfinylaniline was estimated as aniline hydrochloride by decomposition with hydrochloric acid: yield 2.1 g (0.016 mol). The previous precipitate was added to 100 ml of water and stirred for 10 min. The white solid was collected and dried under reduced pressure to give 6.8 g (0.017 mol) of bis-*p*-chlorobenzoyl dithiosulfite (**2b**), mp 129–130 °C. The aqueous solution was evaporated under reduced pressure to give 4.3 g (0.033 mol) of aniline hydrochloride.

Reaction of 1b with a 2 Molar Quantity of Amines. A solution of 8.2 g (0.0325 mol) of **1b** in 20 ml of THF was added to a stirred solution of 6.0 g (0.065 mol) of aniline in 50 ml of ether at −30 °C during 1 h. The reaction mixture was stirred at −30 °C for an additional 2 h and then the precipitated material was filtered and the filtrate was evaporated. Residual solid was combined with the precipitate and stirred with 100 ml of water for 10 min. The light yellow solid was collected and recrystallized with EtOH to yield 6.7 g (0.029 mol) of *p*-chlorobenzanilide, mp 194 °C (lit. 194 °C), and 0.6 g of sulfur. The aqueous solution was evaporated to give 4.1 g (0.032 mol) of aniline hydrochloride. Diethylamine (4.1 g, 0.056 mol) reacted similarly with **1b** (7.1 g, 0.028 mol) to give 2.9 g (0.026 mol) of diethylamine hydrochloride, 0.4 g of sulfur, and an oil. The oil was distilled to give 3.8 g (0.018 mol) of *N*-diethyl-*p*-chlorobenzamide, bp 120–121 °C (0.4 mm) [lit.[6] 115 °C (0.2 mm)].

Reaction of 1b with Carboxylic Acids. To a solution of 7.6 g (0.03 mol) of **1b** in 50 ml of ether, a solution of 2.2 g (0.03 mol) of propionic acid in 10 ml of ether was added at −30 °C. After this, a solution of 3.0 g (0.03 mol) of triethylamine in 10 ml of ether was added dropwise over a period of 1 h. Stirring was continued for an additional 1 h and then the temperature of the mixture was allowed to rise to −10 °C. The precipitated material was filtered and the filtrate was distilled to yield 1.2 g (62%) of propionic anhydride, bp 77–78 °C (40 mm). The precipitate was treated with 100 ml of water for 10 min, filtered, and dried to give 5.8 g (99%) of **2b.** The aqueous solution was evaporated to give 4.0 g (97%) of triethylamine hydrochloride. Benzoic acid reacted similarly with **1b** to yield benzoic anhydride (77%) and **2b** (95%).

Reaction of 1 with Potassium Thiocyanate. A solution of 8.0 g (0.031 mol) of **1b** in 30 ml of THF was added to a suspension of 3.0 g (0.031 mol) of KSCN in 70 ml of THF at 0 °C during 2 h. Soon after, the reaction mixture became colored yellow to orange. Stirring was continued for an additional 2 h and then the reaction mixture was filtered. The filtrate was distilled to give 1.5 g (24%) of *p*-chlorobenzoyl isothiocyanate: bp 102–103 °C (0.2 mm) [lit.[8] 114–118 °C (0.35

mm)]; ir $\nu_{C=O}$ 1680, ν_{NCS} 1980 cm^{-1}. In a similar way **1a** gave benzoyl isothiocyanate: bp 130 °C (12 mm) [lit.[8,9] 115 °C (2.2 mm), 133–137 °C (18 mm)]; ir $\nu_{C=O}$ 1685, ν_{NCS} 1970 cm^{-1}; yield 30%.

Registry No.—**1a**, 41118-54-1; **1b**, 59318-25-1; **5a**, 59318-26-2; thionyl chloride, 7719-09-7; *p*-chlorothiobenzoic acid, 31143-03-0; *p*-chlorobenzoyl *p*-chlorophenyl disulfide, 59318-27-3; bis-*p*-chlorobenzoyl trisulfide, 59318-28-4; bisethoxythiocarbonyl disulfide, 502-55-6; dimethylammonium dimethyldithiocarbamate, 598-64-1; *N*-dimethyl-*p*-chlorobenzamide, 14062-80-7; diethylammonium diethyldithiocarbamate, 1518-58-7; *N*-diethyl-*p*-chlorobenzamide, 7461-38-3; potassium thiocyanate, 333-20-0; *p*-chlorobenzoyl isothiocyanate, 16794-67-5; benzoyl isothiocyanate, 532-55-8; thiophenol, 108-98-5.

References and Notes

(1) S. Motoki and H. Satsumabayashi, *J. Org. Chem.*, **38**, 3654 (1973); **39**, 3617 (1974).
(2) L. Field and W. B. Lacefield, *J. Org. Chem.*, **31**, 3555 (1966).
(3) C. Whitby, *Can. J. Res.*, **2**, 151 (1930).
(4) L. H. Little, G. W. Poling, and J. Leja, *Can. J. Chem.*, **39**, 745 (1961).
(5) A. E. Kulikva, E. N. Zil'berman and F. A. Ekstrin, *Zh. Vses. Khim. O.va*, **11**, 704 (1966).
(6) E. T. McCabe, W. F. Barthel, S. T. Gertler, and S. A. Hall, *J. Org. Chem.*, **19**, 493 (1954).
(7) C. J. Pouchert, "The Aldrich Library of Infrared Spectra", Aldrich Chemical Co., Milwaukee, Wis., 1970, p 858.
(8) E. Profft, H. Teubner, and W. Weuffen, German Patent 74 030 (1970); *Chem. Abstr.*, **74**, 99668m (1971).
(9) J. C. Ambelang and T. B. Johnson, *J. Am. Chem. Soc.*, **61**, 632 (1939).

Acid Catalysis in Dimethyl Sulfoxide Reactions. A Generally Unrecognized Factor[1a]

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Strong acids, generated in situ, are effective catalysts for the oxidation of epoxides and benzyl alcohol, the dehydration of tertiary alcohols, and the conversion of acetamide to bis(acetamido)methane in Me_2SO at elevated temperatures (100–190 °C). The reactions are completely inhibited if excess sodium carbonate or other freshly prepared bases (sodium *n*-octoxide or potassium *tert*-butoxide) are present. The acids, the presence of which has usually gone unrecognized, form either by thermolysis of refluxing Me_2SO in air or oxygen or by interaction of free radicals derived from decomposing hydroperoxides or peroxides with Me_2SO. If an efficient radical trapping agent (acrylonitrile) is present during reaction, acid formation is drastically reduced. The acids formed have been isolated by extraction with a solvent-soluble basic ion-exchange resin and identified as sulfuric and methanesulfonic acids.

In many reactions involving dimethyl sulfoxide (Me_2SO) as a reactant and/or solvent without added acid catalysts, the nature of the reactants and products, the experimental conditions, and the obvious analogies to related reactions that normally require strong acids when carried out in other media suggested to us that strong acid catalysis must be playing a critical role. When the present work was initiated in 1966 acid catalysis had neither been demonstrated nor apparently even considered. Since then it has been reported that acid formation may occur in the oxidation of amine salts on prolonged heating in Me_2SO[2] and acid catalysis is involved in the thermolysis of Me_2SO.[3] Beginning with the putative free-radical oxidation of epoxides by Me_2SO,[4] we reinvestigated several of these reactions to attempt to resolve the following questions: (1) Are strong acids formed in situ during these reactions? (2) If acids are formed, how do they originate and can they be isolated and identified? (3) Are the reactions in fact acid catalyzed, failing in the absence of the acids and proceeding normally when the acids are deliberately added?

Results and Discussion

Unrecognized Strong Acid Catalysis in the Me_2SO Oxidation of Epoxides. The reaction of Me_2SO with styrene oxide at 100 °C (molar ratio 6:1) in the presence of a dry air stream was repeated as originally described.[4] The epoxide was consumed and phenacyl alcohol (25%) was formed as reported. Titration of the aqueous extract of the reaction mixture with base, however, revealed the presence of a small quantity of strong acids (2.5×10^{-2} equiv per mole of epoxide originally present). Addition of barium chloride solution showed the presence of sulfate ion. The reaction was then repeated in the presence of *tert*-butyl hydroperoxide (air absent). Again, oxidation of styrene oxide to phenacyl alcohol occurred and strong acids were shown to be formed (ca. $4–6 \times 10^{-2}$ equiv per mole of hydroperoxide). When both reactions were repeated in the presence of an excess of sodium carbonate, *no* phenacyl alcohol was formed; sulfate ion was shown to be present in the aqueous phases.

We[5] and others[6] have shown that the Me_2SO oxidation of epoxides to α-ketols is catalyzed by strong acids. Since we have now demonstrated that strong acids are formed during the Me_2SO oxidation reaction in air and with hydroperoxide, and the oxidation of the epoxide is completely inhibited in the presence of sodium carbonate, we conclude that it is the strong acids formed in these reactions that are the oxidation catalysts and not oxygen or *tert*-butyl hydroperoxide. The mechanism of the acid-catalyzed Me_2SO oxidation of epoxides, therefore, can be assumed to be that proposed earlier by us;[5] the overall process does not involve free radicals except as intermediates in the formation of the acid catalysts, in contrast to an earlier conclusion.[4] We have also demonstrated that the well-known free-radical source, di-*tert*-butyl peroxide, which decomposes in Me_2SO at 100–120 °C, does not produce strong acids in an inert atmosphere and it is not a catalyst for the oxidation of epoxides at that temperature. (At 155 °C, however, even in an inert atmosphere, strong acids do form but that temperature is well above that required in epoxide oxidations.)

Origin of Strong Acids in Epoxide–Me_2SO Reactions. In air, all three components of the reaction mixture (Me_2SO, epoxide, air) are necessary for the formation of the strong acid catalyst. Thus, when styrene oxide is heated in air under the usual reaction conditions but in the *absence* of Me_2SO, no strong acids are produced.[7] When Me_2SO is added to this preoxidized styrene oxide and the reaction is then continued in the *absence* of air, little if any oxidation of epoxide to phenacyl alcohol occurs. Similarly, when air is bubbled

through Me_2SO alone under the usual reaction conditions (100 °C), no acids are produced; addition of styrene oxide to the pretreated Me_2SO and continuation of the reaction in the *absence* of air yields only traces of oxidation products.

In the reaction of styrene oxide with Me_2SO and *tert*-butyl hydroperoxide at 100 °C, the strong acid catalysts form by interaction of Me_2SO with the hydroperoxide.[8] Thermal decomposition of *tert*-butyl hydroperoxide in Me_2SO for 16 h at 100 °C yields 0.4–0.5 equiv of strong acid per mole of hydroperoxide used, a substantial quantity of acid. Addition of styrene oxide to the acidic Me_2SO solution and continuation of the reaction at 100 °C yields phenacyl alcohol, as expected. Benzoquinone, a known radical scavenger, added at this point, has no effect on the epoxide oxidation. All of the observations just discussed support the conclusion that the strong acids resulting from the hydroperoxide–Me_2SO reaction are the catalysts for the epoxide oxidation and not the hydroperoxide.

The finding that acids are formed from Me_2SO and *tert*-butyl hydroperoxide suggests that the acids formed in the Me_2SO–styrene oxide–air reaction at 100 °C arise by reaction of Me_2SO with hydroperoxides derived from the epoxide. Epoxides, in common with other ethers, are autoxidized to hydroperoxides. The original report[4] that no oxygen is consumed in the Me_2SO–epoxide–air reaction presumably did not take into account the relatively insignificant amount of oxygen that would be required to produce sufficient acid via hydroperoxide to effect catalysis.[9]

Identity of the Strong Acids. When Me_2SO–epoxide–air or *tert*-butyl hydroperoxide oxidation reaction mixtures are diluted with water and treated with aqueous barium chloride, water-insoluble precipitates form suggesting the presence of sulfur acids. These acids were separated by modifying an earlier described analytical technique for the spectroscopic (ir, uv) identification of acids produced in base-catalyzed autoxidations in Me_2SO.[10,11] In the modified method, the acids are directly extracted into a water-immiscible solvent from an aqueous Me_2SO solution by the basic ion-exchange resin, Amberlite LA-2, reportedly a mixture of long-chain aliphatic amines, which forms weakly bonded salts with strong acids.[12a] The success of our modification lies in the discovery that, after separation of the acid-containing resin solution from the aqueous phase, the acids can be easily separated from the resin as phenylhydrazinium salts. On addition of phenylhydrazine, these salts either precipitate or are extracted from the resin solution with water. Further separation and identification of the salts is then carried out using conventional techniques. (Blank runs with the resin, solvents, Me_2SO, and water show no strong acid.)

The strong acids formed by reaction of Me_2SO with *tert*-butyl hydroperoxide are sulfuric and methanesulfonic acids.[12b] Other reaction products identified are *tert*-butyl alcohol, isobutene, acetone, and dimethyl sulfone, the last being the major product isolated (60–65%, based on hydroperoxide consumed). Other pertinent observations are (a) strong acid formation in the reaction of Me_2SO with *tert*-butyl hydroperoxide occurs both in the presence and absence of oxygen, although considerably more acid forms when oxygen is present, suggesting that autoxidation may be one but not the only reaction responsible for acid formation; (b) the yield of acids is reduced by a factor of 25 when the Me_2SO–hydroperoxide reaction is carried out in the presence of acrylonitrile, an effective radical scavenger (molar ratio of acrylonitrile to hydroperoxide 9:1), that forms polyacrylonitrile; and (c) the reaction of dimethyl sulfone with hydroperoxide yields less than one-tenth the acid formed from Me_2SO–hydroperoxide, indicating that the sulfone is not a necessary intermediate in the conversion of sulfoxide to acid.

Unrecognized Strong Acid Catalysis in the Me_2SO Oxidation of Benzyl Alcohol. The similarity between the presumed free-radical oxidation of epoxides by Me_2SO and the free-radical mechanism suggested for the related Me_2SO oxidation of benzyl alcohols to aldehydes[13–16] prompted us to reexamine the latter reaction at 175–190 °C, the temperature range ordinarily used for that oxidation. When a solution of benzyl alcohol in Me_2SO (molar ratio 1:7.6) is saturated with oxygen by flushing with a rapid dry air stream for several minutes and then heated at 190 °C in an NMR tube for 2 h, a 30–35% yield of benzaldehyde is observed, in essential agreement with the original report. However, repetition of the experiment but with sodium carbonate present from the start (molar ratio to benzyl alcohol 1:1) produces no detectable benzaldehyde (NMR).

Repetition of the latter experiment (excess sodium carbonate present) on a small preparative scale at 175 °C for 24 h while a continuous air stream is passed through the mixture produces no benzaldehyde (ir, NMR). Workup of the reaction mixture yields a product whose ir is virtually identical with that of pure benzyl alcohol with only trace absorption at 1700 cm^{-1}. Distillation gives fractions containing only traces of benzaldehyde (ir, NMR); benzaldehyde 2,4-dinitrophenylhydrazone is obtained in a yield of <0.01%. Omission of the sodium carbonate but retention of the air stream produces a steady increase in benzaldehyde, and titration of the reaction mixture indicates that about 2×10^{-3} equiv of strong acid are formed per mole of alcohol originally employed.

As originally reported[13–16] and verified by us,[5] refluxing a solution of benzyl alcohol in Me_2SO containing di-*tert*-butyl peroxide (molar ratio 1:7:0.2) under dry nitrogen for 19 h yields appreciable benzaldehyde (30–35%). After only 3 h, however, the reaction mixture already contains strong acids (3.6×10^{-3} equiv per mole of alcohol and 3.7×10^{-2} equiv per mole of peroxide). Repetition of the experiment with sodium carbonate present (ratio to benzyl alcohol 1:1) produces no detectable benzaldehyde (ir).

As with *tert*-butyl hydroperoxide, it was found that strong acids form when a mixture of Me_2SO and di-*tert*-butyl peroxide (molar ratio 5:1) is heated (155 °C) in an inert atmosphere. As before, the acids were identified as sulfuric and methanesulfonic acids. Other products formed are *tert*-butyl alcohol, isobutene, and dimethyl sulfone (9×10^{-3} mol/mol peroxide). Acrylonitrile (molar ratio to peroxide 12:1), as in the *tert*-butyl hydroperoxide reaction, inhibits acid formation by a factor of 13 and is converted to polymer. Thus, reaction of Me_2SO with peroxide or hydroperoxide yields the same strong acids via a process that most probably involves free radicals.

In the light of these experiments, we conclude that the acids formed in situ in the benzyl alcohol oxidations are responsible for the observed catalysis, as in the epoxide oxidations already discussed. Unlike the epoxide reactions, however, it had not been shown that known strong acids deliberately added are effective catalysts for the alcohol oxidation. Consequently, solutions of benzyl alcohol in Me_2SO (molar ratio 1:7.7) were added to a series of NMR tubes containing no acid, sulfuric or methanesulfonic acids, or "prereacted" Me_2SO–di-*tert*-butyl peroxide (molar ratio 5:1) that had been heated at 155–160 °C for 4 h in an argon atmosphere. All the solutions were purged with argon for 15 min and then heated at 190 °C for up to 7 h, with periodic NMR monitoring of benzaldehyde formation. Results are summarized in Table I.

As Table I shows, sulfuric and methanesulfonic acids are catalysts for the benzyl alcohol oxidation, as are the acids formed by the reaction of Me_2SO with di-*tert*-butyl peroxide at 155 °C. Sulfuric acid is the most efficient catalyst studied. Benzaldehyde is stable on heating in Me_2SO[14] even with oxygen present.

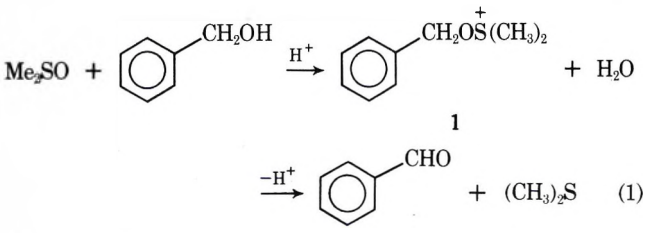
From the above evidence and by analogy with similar oxy-

Table I. Benzyl Alcohol Oxidation to Benzaldehyde by Me_2SO

Acid catalyst	Equiv acid/mol alcohol	Yield of benzaldehyde, %[a]
None		2[b]
Methanesulfonic	3.1×10^{-2}	18
Prereacted Me_2SO–t-Bu_2O_2	4.3×10^{-2}[c]	33
Sulfuric acid	5.5×10^{-3}	43
	7.5×10^{-2}	67

[a] Molar ratio benzyl alcohol to Me_2SO 1:7.7. Reaction time 4 h at 190 °C. Benzaldehyde yields determined by NMR. [b] Yield is 3% after 7 h. [c] Acid content determined by titration. Molar ratio Me_2SO–t-Bu_2O_2 5:1, heated for 4 h at 155–160 °C.

gen transfer reactions involving Me_2SO, the oxidation of benzyl alcohol probably involves acid-catalyzed formation of the benzyloxydimethylsulfonium cation (1) followed by redox decomposition (eq 1). It is unlikely that free radicals are di-



(1)

rectly involved in the oxidation of benzyl alcohol although they play a role in the formation of the acid catalyst. The inhibiting effect of antioxidants on this oxidation observed previously[17a] can now be explained in terms of the ability of the antioxidants to prevent formation of the acid catalyst, as opposed to interruption of a free-radical chain oxidation of the alcohol suggested previously.

"Thermal" Decomposition of Me_2SO. The so-called "thermal" decomposition of Me_2SO is characterized by initial formation of formaldehyde and methanethiol.[18,19] Since the most obvious source of these materials is an acid-catalyzed Pummerer rearrangement of Me_2SO we suspected that strong acids are formed in situ under conditions of "thermolysis". Repetition of the "thermolysis" as originally reported (72-h reflux in air[18]) yields a strongly acidic aqueous solution on workup, a result recently confirmed by others,[3] but the small amount of acid formed precluded identification. In the presence of sodium carbonate, decomposition of Me_2SO is negligible. From these results we conclude that the "thermal" decomposition of Me_2SO is in fact the result of strong acid-catalyzed Pummerer rearrangement.

Repetition of the experiment with oxygen bubbling through the Me_2SO yields 3.9×10^{-3} equiv of acid/mol Me_2SO identified as sulfuric acid by isolation of barium sulfate. When oxygen is excluded either by carrying out the thermolysis in an inert atmosphere (argon) or on a degassed sample, the yield of acid decreases significantly (2.4×10^{-4} equiv/mol Me_2SO in argon; 1.6×10^{-4} equiv/mol Me_2SO in the degassed sample). These results indicate that the major pathway for acid formation in refluxing Me_2SO is an autoxidative one, as has been suggested elsewhere.[3]

To investigate this point further, a low-temperature autoxidation of Me_2SO was carried out by decomposition of AIBN at 80 °C in Me_2SO in an oxygen atmosphere. A mixture of methanesulfonic and sulfuric acids (4.4×10^{-1} equiv total acids/mol AIBN) is produced. No acids form in the absence of oxygen. (It was also found that the sulfuric acid is not derived from methanesulfonic acid by direct autoxidation, as none of the former is produced by decomposition of AIBN in methanesulfonic acid under oxygen.)

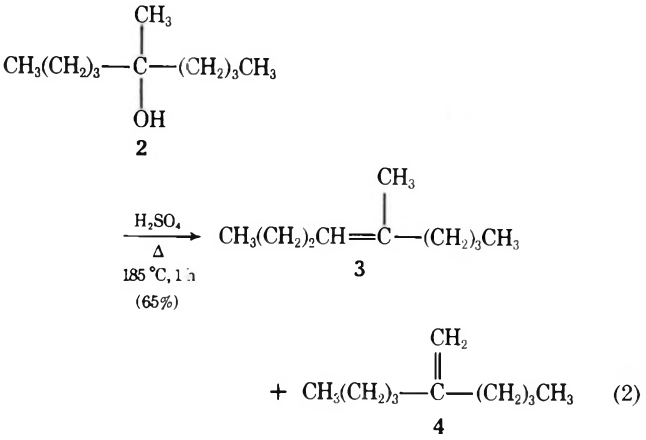
Our conclusion, therefore, is that the acids found on thermolysis of Me_2SO arise from Me_2SO autoxidation, at least in part. A likely pathway involves initial formation of hydroperoxides, either from Me_2SO itself, from minor impurities initially present, or from other components of a reaction mixture (see below). The formation of acid could then proceed as in the case of added hydroperoxide or epoxide-derived hydroperoxide.

Whether the small amount of acid found on thermolysis under nominally oxygen-free conditions arises as a result of the adventitious presence of oxygen or other impurities, e.g., hydroperoxides, or whether another distinct mechanism of acid formation is operative is undetermined. It is now clear from our studies, however, that strong acids are formed when Me_2SO is vigorously heated (160–190 °C) even in supposedly inert atmospheres and more form when oxygen is present. Consequently, inadvertent acid catalysis should be suspected in any reaction carried out in Me_2SO at high temperatures. To test this conclusion further, we reinvestigated two such reactions, namely, the dehydration of a tertiary alcohol and the conversion of acetamide to bis(acetamido)methane.

Dehydration of Tertiary Alcohols in Me_2SO.[14-16,20,21] This reaction is especially interesting because it is reported that acid catalysis can be ruled out as a factor inasmuch as the yield of olefins from two alcohols is little affected by the presence of the bases sodium n-octoxide or aniline.[15]

We reinvestigated the alcohol dehydration reaction but chose 5-methyl-5-nonanol (2) rather than 5-n-butyl-5-nonanol originally employed because the former, although structurally similar to the latter, is unsymmetrical and offers the possibility of formation of isomeric olefins which might provide additional insight into the nature of the dehydration process. Although not specified in the original publication, a nominally inert atmosphere (argon) was employed in all of the current experiments.

As a control and to calibrate the NMR analytical method, dehydration of neat 2 was conducted at 185 °C for 1 h with sulfuric acid catalysis. A 65% yield of a mixture of *cis*- + *trans*-5-methyl-4-nonene (3) and 2-n-butyl-1-hexene (4) was obtained in a ratio of 19:1 (eq 2). As expected the more highly substituted olefin predominates.



(2)

Dehydration in refluxing Me_2SO (mole ratio Me_2SO:2 10:1) in the absence of added catalyst, carried out for 17 h as originally reported but under argon,[15] gives an approximately 40% conversion to a mixture of olefins 3 and 4 in a molar ratio of 6:1. The aqueous phase obtained during the workup procedure is strongly acidic and gives a positive test for sulfate ($BaCl_2$ solution). Titration of the aqueous phase shows that 1.6×10^{-3} equiv of acid form per mole of 2. No attempt was made to establish whether the products are kinetically or thermody-

namically controlled in either reaction. In both cases, internal olefin predominates even though the ratios of **3** to **4** are not the same.

Repetition of the alcohol–Me_2SO reaction for 30 h but with freshly distilled aniline present (molar ratio **2**:aniline:Me_2SO 1.1:1:10) yields some **3** and **4**, as the literature states,[15,16] but considerable alcohol remains intact. Titration of the aqueous phase obtained in the workup indicates the formation of 8×10^{-3} equiv of strong acid per mole of alcohol; the aqueous phase gives a positive test for sulfate.

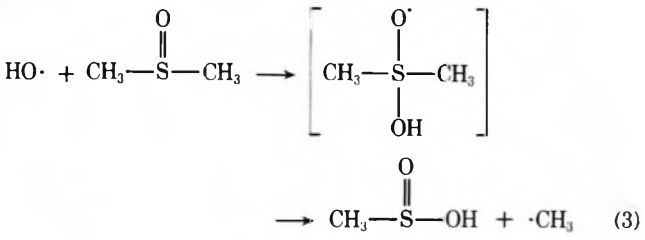
The problem in using aniline as an acid acceptor is that it is a weak base whose presence would not completely inhibit acid catalysis. The use of bases which irreversibly neutralize strong acids is not open to such an objection; therefore, the report that sodium *n*-octoxide does not prevent dehydration is most significant.[15] Repetition of the refluxing Me_2SO–alcohol reaction for 17 h in the presence of freshly prepared sodium *n*-octoxide (mole ratio of alcohol to base varied from 1:1 to 1:0.1) yields no detectable olefins (NMR) and reaction workup yields only a mixture of **2** and 1-octanol, whether the reactions are conducted in air or argon. For confirmation of the role of bases in preventing dehydration, the reactions were repeated using sodium carbonate or potassium *tert*-butoxide; in both cases no olefins could be detected.

We are unable to explain the discrepancy between our results and the earlier literature but our results clearly indicate that the dehydration of tertiary alcohols in refluxing Me_2SO is acid catalyzed; the acid is formed in situ and is comprised, at least in part, of sulfuric acid.

Conversion of Acetamide (5) to Bis(acetamido)methane (6). When **5** is refluxed in Me_2SO in air for 15–20 h, a 50–60% conversion to **6** is obtained (NMR), confirming a literature report in which the atmosphere was not specified.[18] Multiple degassing and freeze–thawing of the Me_2SO–acetamide solution in an argon atmosphere before reaction reduces the conversion to about 15% but does not completely prevent it from taking place. When the reaction is conducted in an oxygen atmosphere, all of the **5** is consumed but a complex product mixture is obtained that could not be analyzed by NMR owing to overlapping signals. However, when the experiment in oxygen is repeated in the presence of sodium carbonate as acid acceptor, only unreacted acetamide is present in the reaction mixture even after extended reaction times (40 h at 185–190 °C). We conclude, therefore, that the conversion of **5** to **6** is acid catalyzed; the acids probably include sulfuric acid although in this case no attempt was made to identify them. The simplest pathway for the overall reaction of **5** to **6** involves formation of formaldehyde by acid-catalyzed decomposition of Me_2SO[18,19] followed by direct condensation of **5** with formaldehyde, although other more complex reaction pathways can be envisioned.[22]

Pathways of Acid Formation in Me_2SO. Numerous free-radical and/or ionic pathways can be written for the formation of sulfuric and methanesulfonic acids from Me_2SO on thermolysis in the presence or absence of oxygen and peroxides or other radical sources. Studies designed to sort out the possibilities unequivocally are outside the scope of this investigation but some data are available.[22]

Our observations on the reaction of Me_2SO with hydroperoxides, either added initially or produced in situ by autoxidation, support a mechanism involving initial homolysis of the hydroperoxide to form hydroxyl radical, followed by its addition to Me_2SO and subsequent decomposition of the adduct (eq 3). This is the sequence that has been observed spectrally (EPR) by other workers.[12b] The inhibitory effect of acrylonitrile on acid formation favors this pathway as opposed to nucleophilic attack of the undissociated hydroperoxide on Me_2SO.[12b] A similar pathway can be written for the reaction of *tert*-butoxy radical (from homolysis of either



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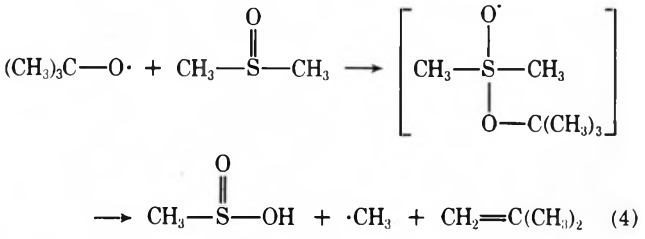
tert-butyl peroxide or *tert*-butyl hydroperoxide) on Me_2SO (eq 4).

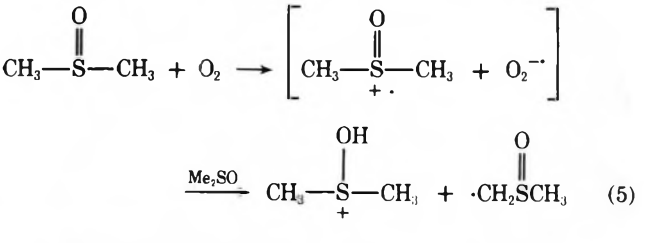


(4)

The methanesulfonic acid isolated presumably arises from the subsequent oxidation (in situ or during workup) of the initially produced methanesulfinic acid.

The sulfuric acid produced could be formed by oxidation of methanesulfinic and/or methanesulfonic acids in processes analogous to the oxidation to the sulfoxide (eq 3 and 4). In support of this concept, it had been shown previously that aqueous hydrogen peroxide and methanesulfonic acid yield sulfuric acid on heating, probably via a free-radical reaction.[17b] We found that heating an aqueous mixture of *tert*-butyl hydroperoxide and methanesulfonic acid in an oxygen-free atmosphere also produces sulfuric acid.

An alternate mechanism for autoxidation of Me_2SO not involving hydroperoxides has been proposed[3] (eq 5 and 6).



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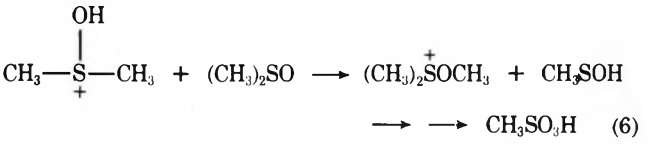

(6)

The formation of methanesulfenic acid from protonated Me_2SO (eq 6) was first postulated to account for the formation of methanesulfonic acid from the reaction of Me_2SO, halide salts, and added acids.[17c] We reinvestigated the Me_2SO–halide–acid reaction using fumaric acid and potassium bromide. When carried out as originally described, the procedure does indeed result in the formation of appreciable quantities of additional acid, as determined by titration of the reaction mixture, and the mixture gives a positive test for sulfate. However, when the halide was omitted we find that no additional acid is produced. Since the reaction indicated in eq 6 requires only the presence of protonated sulfoxide for further acid formation, this negative result makes it unlikely that the pathway shown in eq 6 is operative, either in the Me_2SO–halide–acid reaction or in Me_2SO autoxidation. Since the redox reactions of sulfoxides and halides in acidic media are well known, it is much more likely that the methanesulfonic acid found in the Me_2SO–halide–acid reaction is formed by nucleophilic attack of halide on a methyl group of protonated

Me_2SO rather than by attack by Me_2SO (eq 6). Therefore, we tend to favor a mechanism involving in situ hydroperoxide formation to explain the acid products of Me_2SO autoxidation.

The usually easily autoxidized benzaldehyde is stable on heating in Me_2SO even with oxygen present.[14] This stability may be attributable to the scavenging of peroxy radicals by Me_2SO and/or the immediate destruction by Me_2SO or strong acids derived from it of any peroxy acid or other organic peroxides which catalyze the autoxidation of benzaldehyde.

Whatever the details of the mechanism of acid formation, however, what is clear from our studies is that strong acid catalysis, frequently unrecognized by earlier investigators, is responsible for the success of certain reactions performed in Me_2SO solution. In the presence of strong acids, these reactions are efficient and give high yields of products whereas when the acids are prevented from forming or building up (base present) the reactions are effectively inhibited. Adventitious acid catalysis may also be a factor in a large number of other previously reported related reactions[22] and should be taken into account whenever Me_2SO or structurally related sulfoxides are employed at high temperatures or in the presence of oxidizing agents.

Experimental Section[23]

Me_2SO Oxidation of Styrene Oxide. A. Freshly distilled styrene oxide, bp 104° (50 Torr) (12 g, 0.1 mol), and dry pure Me_2SO (44 g, 0.56 mol) were heated at 100 °C for 20 h while a stream of dried air was passed through the reaction mixture. Methyl sulfide was collected in a dry ice–acetone trap and identified as its mercuric chloride complex. The reaction mixture was poured into ice water (100 ml) and the precipitate was filtered, dried under vacuum, and recrystallized from aqueous ethanol–heptane. Phenacyl alcohol (7), mp 85–87.5 °C (lit.[24] 86 °C) (2.5 g), was obtained; it was spectrally identical (ir, NMR) with an authentic sample. Collection of several more crystal crops and recrystallization resulted in an overall yield of 7 of 25%. Aliquots of the aqueous solution gave the same titer with 0.1 N sodium hydroxide using either phenolphthalein or alizarin red as indicators, indicating that the aqueous phase contained strong acids. Calculation indicated that 2.5×10^{-2} equiv of acid had formed per mole of epoxide.

B. Weighed portions (0.5 g) of stock solution of Me_2SO, styrene oxide, and *tert*-butyl hydroperoxide (molar ratio 5:1:0.1) were heated at 100 °C for up to 20 h in the absence of air. The reaction mixtures exhibited a steady increase in strong acids with time (0.01 N sodium hydroxide titration) and reached a final value of 5.7×10^{-2} equiv of acid per mole of hydroperoxide.

C. Me_2SO (44 g, 0.56 mol) and *tert*-butyl hydroperoxide (0.99 g, 0.01 mol) were mixed at room temperature; no acidic substances formed. After being heated at 100 °C for 16 h, the reaction mixture contained 0.4 equiv of strong acids per mole of hydroperoxide originally present; peroxide content was reduced by 97%. The volatiles collected in a cold trap showed the presence of acetone, *tert*-butyl alcohol, water, and several unidentified minor components (ir, GLC). Styrene oxide (12 g, 0.1 mol) and benzoquinone (0.003 mol) were added at room temperature and the reaction mixture was heated to 100 °C. After only 20 min intense ir absorption (1680 cm^{-1}) characteristic of 7 was observed and it increased with time. The reaction mixture was worked up as in A above and extracted with carbon tetrachloride or chloroform. The solid obtained upon evaporation of solvent was largely 7. The aqueous layer gave a positive test for sulfate with barium chloride solution.

D. When reactions A and C were repeated for 28–48 h but in the presence of anhydrous sodium carbonate[25] (0.1–1 mol per mole of styrene oxide), the ir and NMR spectra showed essentially no changes. Usual workup (aqueous dilution followed by chloroform extraction) yielded a residue of styrene oxide (ir); no absorbances for 7 could be observed. The aqueous phases were acidified with hydrochloric acid and boiled to destroy carbonate; addition of barium chloride solution yielded an insoluble precipitate indicating that sulfate ion was present.

Origin of Strong Acids in Epoxide–Me_2SO Reactions. A. Air was passed through neat styrene oxide (0.1 mol) for 19 h at 100 °C after which the system was flushed with dry nitrogen for 1 h. Aliquots were titrated with 0.1 N NaOH using phenolphthalein or alizarin red; the titer with the former was almost four times that with the latter indicating the presence of a weak acid. Ir showed very weak bands at 3500 and 1680 cm^{-1} charcacteristic of 7. Addition of Me_2SO (0.5 mol) followed by heating at 100 °C under nitrogen for an additional 27 h resulted in only slight increases in intensity at 3500 and 1680 cm^{-1}. Volatiles were collected in a cold trap. The contents of the cold trap consisted of Me_2SO and water.

B. Air was passed through Me_2SO (0.2 mol) at 100 °C for 17 h followed by nitrogen flushing for 0.5 h. Less than 0.05 ml of 0.1 N NaOH was consumed by a 2-g aliquot (phenolphthalein indicator). Styrene oxide (0.04 mol) was then added and heating was continued for an additional 27 h and then 26 h more. Only traces of 7 were formed (ir).

Identification of Strong Acids. A. General Procedure. Me_2SO reaction mixtures were cooled to room temperature and poured into ice water (threefold excess v/v). Solids, if formed, were filtered off for separate examination and the filtrate was multiply extracted with ether (ten extractions, each portion 2:1 v/v ether to aqueous phase). The aqueous phase was then extracted successively with freshly prepared ether solutions of Amberlite LA-2 183 (5% v/v in ether) until the aqueous phase was slightly basic (three to five extractions typically). The aqueous phase was further extracted with several portions of ether and these were combined with the initial Amberlite LA-2 ether extracts. The combined LA-2 extracts were dried over Linde 4A molecular sieves and, after filtration, an ether solution of phenylhydrazine (20% v/v in ether) was added dropwise to the filtrate until no further turbidity was produced. The precipitate was filtered and recrystallized from absolute ethanol or absolute ethanol–ether; the crystalline product was identical with authentic phenylhydrazinium sulfate. The ether filtrate from the initial phenylhydrazine salt precipitation was then multiply extracted with water (five times, each portion 1:1 v/v ether to water). The water was evaporated under reduced pressure (30–40 Torr), and the residual red solid or oil was successively recrystallized from a minimum of absolute ethanol and then absolute ethanol–ether. This procedure usually cleanly separated phenylhydrazinium methanesulfate from any residual phenylhydrazinium sulfate.

B. Me_2SO–*tert*-Butyl Hydroperoxide Reactions. Nitrogen Atmosphere (Preparative Experiment). *tert*-Butyl hydroperoxide (17.5 g of 90% commercial material, 0.175 mol) was added dropwise over several hours to Me_2SO (27.5 g, 0.352 mol) at 100 °C while a stream of dry nitrogen was used to sweep volatile products into a dry ice–acetone cold trap. After 43 h at 100 °C only a faint test for hydroperoxide ($KCNS–FeSO_4$) was obtained. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered and purified by sublimation (ca. 50 °C at 0.5 Torr). The sublimate was triturated with cold ether to remove any contaminating Me_2SO, dried, and recrystallized from ethanol. The solid was dimethyl sulfone, mp 106–109 °C, mmp with authentic sample 108–110 °C. The filtrate of the reaction mixture after extraction of the acidic components as described in A precipitated additional sulfone for a total yield after recrystallization of 60–65%, based on hydroperoxide. The acidic components were separated from the filtrate as described in A. Phenylhydrazinium sulfate: mp 226–230 °C dec; mmp with an authentic sample 230–233 °C dec; ir spectra of the isolated and authentic salts were identical; equiv wt calcd 157, found 157. Phenylhydrazinium methanesulfonate: mp 193–195 °C dec; mmp with an authentic sample 193–195 °C dec (lit.[26] 193–194.5 °C); ir and NMR spectra and TLC R_f values of the isolated and authentic salts were identical; equiv wt calcd 204, found 207.

The contents of the cold trap were fractionally distilled and various components of the mixture were identified by conventional means (GLC, ir, NMR) as *tert*-butyl alcohol, acetone, isobutylene, and water, and traces of hydroperoxide, Me_2SO and sulfone, among others.

Oxygen Atmosphere. Me_2SO (44 g, 0.564 mol) and *tert*-butyl hydroperoxide (0.895 g of 90% pure material, 0.0089 mol) were heated for 24 h at 100 °C in an oxygen atmosphere. The reaction mixture was diluted to a known volume with water and an aliquot was titrated with 0.1 N NaOH; 0.50 equiv of acid per mole of hydroperoxide was formed.

Argon Atmosphere. Repetition of the above experiment but under an argon atmosphere yielded only 0.13 equiv of acid per mole of hydroperoxide (molar ratio of reactants, Me_2SO:*tert*-butyl hydroperoxide 45.8:1).

Effect of Acrylonitrile. Repetition of the above experiment in the presence of freshly distilled acrylonitrile gave a 90% yield of polyacrylonitrile but only 0.0053 equiv of acid per mole of hydroperoxide (molar ratio of reactants, Me_2SO:acrylonitrile:*tert*-butyl hydroperoxide 45.8:9.16:1).

Me_2SO Oxidation of Benzyl Alcohol. A. NMR Experiments. A stock solution of benzyl alcohol (1.08 g, 0.01 mol) in Me_2SO (5.93

g, 0.076 mol) containing DSS (0.05 g) was prepared and portions were added to NMR tubes by means of a syringe. Oxygen was bubbled through the solutions for several minutes and the tubes were then immersed in a bath maintained at 190 °C while oxygen was slowly passed over the contents. Periodically, a tube was removed, cooled to room temperature, and the benzaldehyde conversion was determined by NMR (ratio of the integral of the aromatic proton signal to that of the aldehydic proton singlet at δ 10). After 2 h at 190 °C, a 30–35% conversion to benzaldehyde was obtained. Addition of sodium carbonate (equimolar with respect to benzyl alcohol[25]) to the NMR tube prior to heating resulted in no benzaldehyde formation even though a plentiful supply of oxygen was provided.

B. Preparative Experiments. Results identical with those in A were obtained on a preparative scale. Only traces of benzaldehyde were formed in the presence of air when sodium carbonate was used; the aldehyde yield was estimated to be less than 0.01% (ir, NMR, and isolation of the 2,4-dinitrophenylhydrazone) and the benzyl alcohol was unchanged. In the absence of base, 2×10^{-3} equiv of acid per mole of benzyl alcohol formed after 6 h reaction at 175 °C.

C. *tert*-Butyl Peroxide–Me_2SO–Benzyl Alcohol Reactions. Benzyl alcohol (1.04 g, 0.0096 mol), Me_2SO (5 ml, 0.07 mol), and *tert*-butyl peroxide (0.280 g, 0.002 mol) were refluxed under dry nitrogen with periodic removal of samples for ir examination. From previously determined Beer's law plots on solutions of known concentrations of benzyl alcohol and benzaldehyde, conversion of benzyl alcohol to benzaldehyde was calculated to be about 30% after 19 h. Repetition of this experiment but with sodium carbonate present (1.05 g, 0.01 mol[25]) yielded no benzaldehyde (lower limit of detection by ir less than 2%).

D. Acid-Catalyzed Me_2SO–Benzyl Alcohol Oxidations. The NMR experiments in A were repeated except that (a) all solutions were carefully purged with argon and maintained in an argon atmosphere and (b) known quantities of strong acids were added to the NMR tubes, as shown in Table I.

Me_2SO–*tert*-Butyl Peroxide Reactions. A. Preparative Experiment. *tert*-Butyl peroxide (10.3 g, 0.0704 mol) was added dropwise over a period to Me_2SO (27.5 g, 0.352 mol) maintained under argon at 155–160 °C, the Me_2SO having been sparged with argon at 160 °C for 1 h before beginning the peroxide addition. Heating was continued for 3 h after peroxide addition was complete. The reaction mixture was allowed to cool and then was poured into water (250 ml). The aqueous mixture was filtered and then treated as already described to separate the acidic components which were identified from their phenylhydrazine salts as methanesulfonic and sulfuric acids. The volatile products collected in a dry ice–acetone trap were identified as methyl sulfide, *tert*-butyl alcohol, isobutylene, and what appeared to be acetaldehyde (NMR); other unidentified products were also present.

B. Effect of Acrylonitrile. *tert*-Butyl peroxide (0.590 g, 0.00404 mol), Me_2SO (15.4 g, 0.197 mol), and freshly distilled acrylonitrile (2.64 g, 0.00498 mol) were heated together under argon for 1 h at 155 °C (vigorous refluxing). This resulted in the formation of polyacrylonitrile (2.2 g, 85%); the yield of acid was found by potentiometric titration to be 0.014 equiv per mole of peroxide.

When the experiment was repeated in the absence of acrylonitrile, the yield of acid was 0.181 equiv per mole of peroxide, about 13 times that in the presence of monomer.

C. Effect of Temperature. *tert*-Butyl peroxide (1.46 g, 0.0100 mol) and Me_2SO (2.5 ml, 0.035 mol) were allowed to react under nitrogen at 100–120 °C. After 18–42 h, the titre of a 5-ml aliquot with 0.1 N aqueous sodium hydroxide was 0.1 ml. When the reaction was repeated at reflux temperatures (170–180 °C), however, the titre of a 5-ml aliquot after only 2 h was 3.0 ml and the appearance of the solution indicated pronounced decomposition of Me_2SO.

Autoxidation of Me_2SO Using AIBN. Me_2SO (44.0 g, 0.563 mol) and AIBN (2.05 g, 0.0125 mol) were allowed to react under oxygen at 80 °C for 20 h. Another portion of AIBN (2.05 g, 0.0125 mol) was then added, and the reaction was allowed to continue for another 24 h. The reaction mixture was poured into water and the resulting precipitate was collected by filtration. The precipitate was recrystallized from water and sublimed (80 °C at 0.05 Torr) to give tetramethylsuccinonitrile, mp 170–171 °C (lit.[27] 169 °C). The filtrate was treated to separate the acids present, which were identified via their phenylhydrazinium salts as methanesulfonic and sulfuric acids. In a similar experiment, the yield of acids was found by titration to be 0.440 equiv per mole of AIBN. When the reaction was carried out on a degassed sample (in an apparatus fitted with a Bunsen valve which allowed the nitrogen produced by the decomposition of AIBN to escape but which prevented oxygen from entering), no acid could be detected by titration with 0.01 N sodium hydroxide.

Attempted Autoxidation of Methanesulfonic Acid Using AIBN. AIBN (0.820 g, 4.99×10^{-3} mol) was decomposed by heating in methanesulfonic acid (15.0 g, 0.156 mol) at 80 °C for 17 h under oxygen. Treatment of the reaction mixture with aqueous barium chloride (1 ml of a saturated solution) resulted in the formation of lustrous platelets of barium methanesulfonate which redissolved completely on addition of sufficient water, indicating the absence of barium sulfate and hence sulfuric acid. Previous experiments using various dilutions of sulfuric acid had shown that a minimum concentration of 2.0×10^{-3} mol/l. of sulfuric acid could be detected in the presence of 50% aqueous methanesulfonic acid using this method.

"Thermal" Decomposition of Me_2SO. Me_2SO was vigorously flushed with oxygen at room temperature and then heated to reflux (190 °C) for 72 h while a slow stream of oxygen was passed through it. The internal temperature fell to 160 °C because of the presence of lower boiling decomposition products and a white coating, presumably polyformaldehyde, covered the surface of the container. The bright yellow Me_2SO solution was diluted with 1.5 volumes of water and an aliquot was titrated with 0.1 N sodium hydroxide (phenolphthalein). The acids formed amounted to 3.9×10^{-3} equiv per mole of Me_2SO. Treatment of the aqueous system with barium chloride solution yielded barium sulfate, identified by x-ray analysis. When the thermolysis was conducted in an argon atmosphere the yield of acid was reduced to 0.24×10^{-3} equiv per mole of Me_2SO. Repetition of the thermolysis with a degassed sample yielded 0.16×10^{-3} equiv of acid per mole of Me_2SO. In the presence of sodium carbonate, decomposition of Me_2SO is negligible as evidenced by the failure to obtain volatile decomposition products and polyformaldehyde.

Dehydration of 5-Methyl-5-nonanol (2). A. Sulfuric Acid Catalyst. Neat **2** (1.6 g, 0.0010 mol) containing a drop of concentrated sulfuric acid was refluxed for 1 h. The reaction mixture was poured into water (30 ml), neutralized with aqueous base, and extracted with *n*-hexane (3 × 20 ml). The hexane solution was washed with water (2 × 10 ml) and dried (Na_2SO_4). Evaporation of the solvent at 25–30 °C yielded a yellow, oily residue (0.94 g, 65% yield). Based on chemical shifts, multiplicities, and integration,[28] and by comparison with spectra of related olefins,[29] the signals in the olefinic region were assigned to *cis*- and *trans*-5-methyl-4-nonene (δ 5.61) (**3**) and 2-*n*-butyl-1-hexene (δ 4.70) (**4**). The ratio of **3**:**4** was 19:1.

B. In Refluxing Me_2SO. A solution of **2** (1.27 g, 0.00807 mol) in Me_2SO (6.54 g, 0.0831 mol) was refluxed for 17 h in an argon atmosphere; the reaction mixture separated into two phases. The mixture was poured into water (70 ml) and an aliquot was titrated with 0.1 N NaOH. The yield of acid was 1.6×10^{-3} equiv per mole of alcohol. Further workup as in A gave a light yellow oil (0.33 g, 40% yield) whose NMR spectrum (neat) was qualitatively identical with that of the product from the sulfuric acid catalyzed dehydration; the ratio of **3**:**4** was 6:1, however. The aqueous phase gave a positive test for sulfate ion with barium chloride solution.

C. In Refluxing Me_2SO with Aniline. Me_2SO (11.2 g, 0.143 mol), **2** (2.17 g, 0.0140 mol), and freshly distilled aniline (1.15 g, 0.0123 mol) were heated at reflux for 50 h in an argon atmosphere. Workup yielded a dark oil which consisted largely of unreacted **2** and aniline with **3** and **4** as minor products (NMR). The aqueous phase gave a positive test for sulfate and was found to contain 8.4×10^{-3} equiv of acid per mole of alcohol. The same qualitative results were obtained when the reaction was conducted in air.

D. In Refluxing Me_2SO with Bases. Me_2SO (1.82 g, 0.0233 mol), **2** (4.22 g, 0.0267 mol), and freshly prepared sodium *n*-octoxide (4.00 g, 0.0261 mol) were heated under argon for 17 h at 185 °C; olefin formation could not be detected. Workup yielded a yellow oil (5.6 g) which consisted exclusively of **2** and 1-octanol (NMR). The same results (olefins absent) were obtained when the ratio of **2** to base was 10:1; when the ratio of **2** to Me_2SO was 1:10 and air was not excluded; and in the presence or absence of oxygen when sodium carbonate or potassium *tert*-butoxide were the bases.

Acetamide (5) Condensations in Me_2SO. A. Air. A solution of acetamide (1.03 g, 0.0174 mol) in Me_2SO (7.07 g, 0.091 mol) in an NMR tube was heated to 190 °C for 17 h; conversion of **5** to **6** was 50–60%. The percent conversion was calculated from NMR by comparing the integrated value of the methylene protons (t, δ 4.40) with that of the combined values of the methyl signals of **6** (s, δ 1.81) and **5** (s, δ 1.79). The NMR assignments were verified by comparison with the NMR spectra of authentic materials in Me_2SO. The yield of acids formed was 0.15 equiv per mole of acetamide.

B. Argon Atmosphere. Merely flushing the reaction mixture of A with argon at room temperature for 6 h prior to heating caused no change in conversion of **5** to **6**. A solution of **5** in Me_2SO in an NMR tube capped with a rubber septum was frozen in dry ice–acetone while reducing the pressure through a hollow needle to 0.05 Torr followed

by thawing under positive argon pressure. The freeze–thaw process was repeated four times and the solution was then heated to 190 °C for 23 h. NMR indicated a 16% conversion of **5** to **6**.

C. Sodium Carbonate. When an equimolar quantity of sodium carbonate[25] to **5** was present during the heating process (42 h), **6** was not formed either in the presence or absence of oxygen.

Reaction of Methanesulfonic Acid and *tert*-Butyl Hydroperoxide. A mixture of methanesulfonic acid (0.200 g, 0.00208 mol), *tert*-butyl hydroperoxide (0.220 g of 90% material, 0.00220 mol), and water (10 g) was degassed and then allowed to react under helium at 95 °C for 15 h. Treatment of the reaction mixture with aqueous barium chloride (1 ml of a saturated solution) resulted in the formation of a mixture of lustrous platelets of barium methanesulfonate, which dissolved on dilution with water, and a finely divided white precipitate, presumably barium sulfate, which remained insoluble, indicating the presence of sulfuric acid.

Reaction of Me_2SO with Fumaric Acid. A. In the Presence of Potassium Bromide. Me_2SO (5.05 g, 0.0647 mol), fumaric acid (0.0667 g, 5.74×10^{-4} mol), and potassium bromide (0.116 g, 9.75×10^{-4} mol) were allowed to react in air for 0.5 h at reflux (bath temperature maintained at 195 °C). Refluxing quickly became very vigorous, and pronounced decomposition of the Me_2SO was evident. The mixture separated into a liquid upper phase and a gel. The contents of the flask were transferred quantitatively into water (35 ml) and the acid content was determined by titration. The acid formed in excess of the fumaric acid orginally present was found to be 4.31×10^{-2} equiv per mole of Me_2SO. The reaction mixture also gave a strong positive test for sulfate with aqueous barium chloride.

B. In the Absence of Potassium Bromide. When the reaction was repeated in the absence of potassium bromide, vigorous refluxing was not evident until the end of the 0.5-h reaction period. The reaction mixture yellowed slightly, but decomposition of the Me_2SO was not pronounced. Titration revealed no acid in excess of that originally present. Only a faint opalescence was observed on treatment with aqueous barium chloride. The results were the same whether the reaction was carried out on a degassed sample under argon, in air, or in an oxygen atmosphere.

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Registry No.—**2**, 33933-78-7; **5**, 60-35-5; sodium carbonate, 7542-12-3; methanesulfonic acid, 75-75-2; sulfuric acid, 7664-93-9; Me_2SO, 67-68-5; styrene oxide, 96-09-3; *tert*-butyl hydroperoxide, 75-91-2; benzyl alcohol, 100-51-6; *tert*-butyl peroxide, 110-05-4; fumaric acid, 110-17-8.

References and Notes

(1) (a) Chemistry of Epoxides. 32. Part 31: T. M. Santosusso and D. Swern, *J. Org. Chem.*, **40**, 2764 (1975). (b) In partial fulfillment of the requirements for the Ph.D. degree, Temple University, 1975.
(2) V. J. Traynelis and R. H. Ode, *J. Org. Chem.*, **35**, 2207 (1970).
(3) D. L. Head and D. G. McCarty, *Tetrahedron Lett.*, 1405 (1973).
(4) T. Tsuji, *Tetrahedron Lett.*, 2413 (1966); *Q. Rep. Sulfur Chem.*, **3**, 184 (1968).
(5) T. M. Santosusso and D. Swern, *Tetrahedron Lett.*, 4261 (1968); 4255 (1974).
(6) T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1965).
(7) A small amount of benzoic acid is formed by autoxidation of styrene oxide.
(8) Strong acid formation does not occur at room temperature.
(9) In a typical experiment using 0.1 mol of epoxide, the volume of oxygen absorbed could be as little as 60 ml (STP), based on the 2.5×10^{-2} equiv of acid formed per mole of epoxide. This is to be contrasted with the approximately 2.2 l. (as a minimum) that would be required if the epoxide were undergoing conversion to α-ketol solely by autoxidation, a pathway that the original investigator[4] was presumably interested in evaluating.
(10) H. Pokinir, T. Wallace, and J. Hofmann, *Anal. Chem.*, **35**, 681 (1963).
(11) T. J. Wallace, *J. Org. Chem.*, **30**, 4017 (1965).
(12) (a) M. Dolinsky and L. Stein, *Anal. Chem.*, **34**, 127 (1962). (b) Recently it was shown that chemically produced hydroxyl radicals react with Me_2SO at ambient temperatures to produce acidic products: B. C. Gilbert, R. O. C. Norman, and R. C. Sealy, *J. Chem. Soc., Perkin Trans. 2*, 303 (1975), and references cited therein.
(13) W. H. Clement, T. J. Dangieri, and R. W. Tumas, *Chem. Ind. (London)*, 755 (1969).
(14) V. J. Traynelis and W. L. Hergenrother, *J. Am. Chem. Soc.*, **86**, 298 (1964).
(15) V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, **29**, 123 (1964).
(16) V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962).
(17) (a) W. H. Clement, T. J. Dangieri and R. W. Tuman, *Chem. Ind. (London)*, 755 (1969); (b) H. T. Hookway and B. Selton, *J. Phys. Chem.*, **62**, 493 (1958); (c) C. T. Chen and S. J. Yan, *Tetrahedron Lett.*, 3855 (1969).
(18) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, 29, 221 (1964).
(19) W. S. MacGregor, *Q. Rep. Sulfur Chem.*, **3**, 149 (1968).
(20) G. Gelli, A. Maccioni and M. Secci, *Ann. Chim. (Rome)*, **55**, 592 (1965).
(21) For a general discussion of the E_1 reaction of alcohols, see W. H. Saunders, Jr., in "The Chemistry of Epoxides", S. Patai, Ed., Interscience, New York, N.Y., 1964.
(22) For more extensive and speculative discussion of reaction mechanisms consult Ph.D. thesis of T.M.S., Temple University, 1975. The thesis contains an extensive bibliography.
(23) Starting materials were the purest grades purchasable. Most of them were used as received after confirming their purity by physical (melting point, TLC, ir, NMR, uv) and chemical methods. Purification of other starting materials is given under the appropriate experiments. Solvents were dried and purified by established methocs. See J. A. Riddick and W. B. Bunger, "Organic Solvents", Wiley-Interscience, New York, N.Y., 1970. Equipment used has been described: Y. Hayashi and D. Swern, *J. Am. Chem. Soc.*, **95**, 5205 (1973). Elemental analyses were by Micro-Analysis, Inc., Wilmington, Del. Titrations of Me_2SO reaction mixtures for acid content were conducted by first diluting the sample with a large excess of water which had been previously neutralized if necessary.
(24) R. Shriner, R. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1964.
(25) The quantity of sodium carbonate employed is expressed as the initial charge but since it is only partially soluble and is never completely consumed, its actual concentration or extent of consumption is unknown.
(26) P. H. Latimer and R. W. Bost, *J. Am. Chem. Soc.*, **59**, 2501 (1937). We have observed that the methanesulfonate salt also forms a polymorph, mp 206–208 °C.
(27) G. S. Hammond, C. S. Wu, O. D. Trapp, J. Warkentin, and R. T. Keys, *J. Am. Chem. Soc.*, **82**, 5394 (1960).
(28) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2d ed, Pergamon Press, Oxford, 1969, Chapter 3, and references cited therein.
(29) Sadtler NMR Spectra 8003M, 2004M, 3420M, and Varian NMR Spectra 180.

The Sulfide Group as an Aldehyde Precursor

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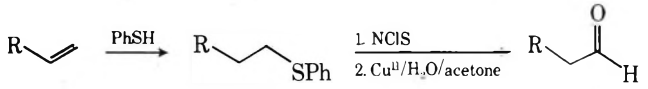
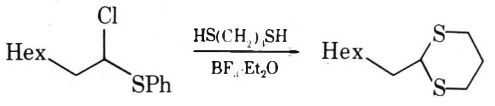
Aldehydes and their derivatives, such as dithianes, occupy a central position in organic synthesis. Accordingly, many synthetic methods have been developed to transform other functional groups into aldehydes or their derivatives but situations still arise where the conventional methods are not satisfactory. In this note we report an alternate sequence of reactions to the well-known hydroboration–oxidation method of transforming a terminal olefin into an aldehyde. Phenyl alkyl sulfides, intermediates in this process, can also be transformed into dithianes and other aldehyde derivatives.



Terminal olefins are readily transformed into phenyl alkyl sulfides by free-radical addition[1] of thiophenol (in appropriately substituted cases, the addition can also be carried out under heterolytic conditions via a Michael reaction). Thus, treatment of 1-octene with thiophenol at 80 °C in the presence of AIBN led to a 97% yield of phenyl octyl sulfide, which was oxidized[2] with 1 equiv of *N*-chlorosuccinimide by refluxing in carbon tetrachloride. After cooling, filtering, and removal of solvent, the crude chloro sulfide was hydrolyzed[3] in the presence of Cu^{II} (to oxidize the thiophenol formed),[7] the resulting octanal was reduced with $LiAlH_4$, and the product, 1-octanol, was isolated in 80% overall yield.

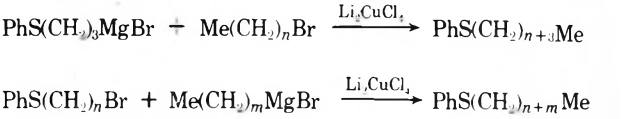
The crude chloro sulfides[8] were found to be useful substrates for the direct preparation of aldehyde derivatives such as dithiolanes and dithianes. Thus, treatment of chloro sulfide 1 with 1,3-propanedithiol and BF_3·Et_2O in methylene chloride



1 2

gave dithiane 2 in 74% yield (see Table I and the Experimental Section for examples of other transformations). The three-step transformation of terminal olefins into alkyl dithianes, important carbonyl synthons,[9] complements the other methods of their preparation and should offer advantages in cases where the aldehyde is not stable, since the free carbonyl compound need not be isolated.

Somewhat surprisingly,[10] 3-bromopropyl phenyl sulfide reacted with magnesium to give a Grignard solution which could be used for functional homologations[11] of alkyl bromides under dilithium tetrachlorocuprate catalysis.[12] Easier to separate product mixtures, however, were obtained by the reverse process. Thus, for example, the catalyzed coupling of pentylmagnesium bromide and 3-bromopropyl phenyl sulfide gave octyl phenyl sulfide in 87% isolated yield.[13]



Experimental Section

Free-radical additions of thiophenol to olefins were carried out under standard conditions,[1] although we found it convenient to use *tert*-butyl perbenzoate as the catalyst in photoinitiated reactions (at 254 nm, quartz tubes, room temperature). Chlorinations of sulfides were performed in CCl_4 with a slight excess of NCIS at room or reflux temperatures, depending upon the sensitivity of the substrate to subsequent reactions (overoxidation or elimination). The crude chloro sulfides were unstable oils, but could be stored in the freezer for several days. The dithianes could be prepared from crude chloro sulfides without the use of BF_3·Et_2O as catalyst, but the reactions were slower and the product mixtures more complex. Representative examples of experimental details are presented below.

Addition of Thiophenol to 1-Octene. A mixture of 1.00 g of 1-octene, 150 mg of AIBN, and 3 ml of thiophenol was heated, under N_2, at 90 °C for 4 h. After cooling, the mixture was diluted with ether, washed with 1 N NaOH solution and water, and dried over Na_2SO_4. The resulting mixture, in 30 ml of ether, was treated with 50 mg of $LiAlH_4$ at room temperature for 6 h (to reduce the diphenyl disulfide formed as a by-product). Usual workup gave 1.91 g (97%) of octyl phenyl sulfide,[14] shown by GLC (DCC 550 at 230 °C) to be more than 98% pure.

Chlorination of Octyl Phenyl Sulfide. Preparation of 1-Octanol. A mixture of 444 mg of octyl phenyl sulfide and 267 mg of NCIS was refluxed, under N_2, for 50 min in 10 ml of CCl_4. After cooling, the mixture was filtered and solvent removed on a rotovac. The residue was refluxed, under N_2, for 10 min with a mixture of 0.2 ml of H_2O, 10 ml of acetone, 680 mg of $CuCl_2$·$2H_2O$, and 680 mg of CuO. After cooling and filtering, the solution was diluted with 3 ml of H_2O and extracted with ether. The organic extract was washed three times with water, dried over Na_2SO_4, and reduced with excess $LiAlH_4$. The crude product was chromatographed on 15 g of silica gel, petroleum ether eluting traces of diphenyl disulfide and 1:1 ether/petroleum ether eluting 209 mg of 1-octanol (80%).

Preparation of 2-Heptyl-1,3-dithiane. The crude chloroalkyl phenyl sulfide, prepared as above from 888 mg of octyl phenyl sulfide, was stirred at room temperature, under N_2, for 10 h with 1.3 ml of 1,3-propanedithiol and 0.12 ml of BF_3·Et_2O in 5 ml of CH_2Cl_2. The

Table I. Conversion of Olefins and Sulfides to Aldehydes, Alcohols, Dithiolanes, or Dithianes[e]

Parent olefin	Sulfide (isolated yield, %)	Oxidation product (isolated yield, %)
Acrylonitrile (107-13-1)	2-Cyanoethyl phenyl sulfide (3055-87-6) (92)	2-Cyanomethyl-1,3-dithiolane (54902-80-6) (52[a])
Styrene (100-42-5)	2-Phenylethyl phenyl sulfide (13865-49-1) (100)	2-Phenylacetaldehyde (122-78-1) (60[b]) 2-Benzyl-1,3-dithiane (31593-52-9) (68[c])
1-Octene (111-66-0)	*n*-Octyl phenyl sulfide (13910-16-2) (97)	1-Octanol (111-87-5) (80[d]) 2-Heptyl-1,3-dithiane (59092-72-7) (74[c])

[a] From crude chloro sulfide, BF_3·Et_2O, and 1,2-ethanedithiol. [b] As DNP. [c] From crude chloro sulfide, BF_3·Et_2O, and 1,3-propanedithiol. [d] From $LiAlH_4$ reduction of crude aldehyde. [e] Registry no. are in parentheses.

crude product was poured into ice–water and extracted with ether. The organic layer was washed with 10% NaOH and water and dried over Na_2SO_4. Removal of solvent gave 863 mg of residue which was chromatographed on 50 g of silica gel. Elution with 1:1 petroleum ether/benzene gave 645 mg (74%) of 2-heptyl-1,3-dithiane (**2**). An analytical sample was prepared by bulb-to-bulb distillation: ir (neat) 6.82, 7.05, 7.86, 8.47, 10.98 μ; ^{1}H NMR (CCl_4) δ 3.96 (t, 1 H, J = 6.3 Hz, 2-dithiane H).

Anal. Calcd for $C_{11}H_{22}S_2$: C, 60.48; H, 10.15. Found: C, 60.37; H, 10.17.

Preparation of 2-Benzyl-1,3-dithiane. A mixture of 516 mg of 2-phenylethyl phenyl sulfide and 350 mg of NClS in 20 ml of CCl_4 was refluxed, under N_2, for 20 min. After cooling and filtering, the solvent was removed on a rotovac to give 583 mg of chloro sulfide, formed quantitatively by NMR (CCl_4) δ 3.27 (d, 2 H, J = 7.0 Hz) and 5.28 (t, 1 H, J = 7.0 Hz). The product and 1 ml of 1,3-propanedithiol in 20 ml of CH_2Cl_2, under N_2, was cooled to 0 °C and 0.5 ml of BF_3-Et_2O was added. The resulting mixture was stirred at room temperature overnight, then diluted with ether, washed with 10% NaOH solution and water, and dried over Na_2SO_4, and solvent was removed. The residue was chromatographed on silica gel with a 1:1 petroleum ether/benzene mixture to give 344 mg (68%) of the dithiane.[15]

Preparation of 2-Cyanomethyl-1,3-dithiolane. A mixture of 1.039 g of 2-cyanoethyl phenyl sulfide,[16] 0.850 g of NClS, and 25 ml of CCl_4, under N_2, was refluxed for 30 min. The usual workup gave 1.314 g of chloro sulfide, 80% pure by NMR. A mixture of 1.060 g of the crude chloro sulfide, 1.3 ml of 1,2-ethanedithiol, and 1.0 ml of BF_3-Et_2O in 5 ml of CH_2Cl_2 was stirred at room temperature for 24 h. The usual basic workup gave 1.16 g of crude product which was chromatographed on 30 g of silica gel. Elution with 1:1 petroleum ether/benzene followed by bulb-to-bulb distillation gave 405 mg (52%) of 2-cyanomethyl-1,3-dithiolane.[17]

Preparation of 3-Bromopropyl Phenyl Sulfide and 4-Bromobutyl Phenyl Sulfide. A mixture of 22 g of thiophenol, 100 g of 1,3-dibromopropane, 13 g of NaOH, 200 ml of H_2O, 200 ml of PhH, and 1.0 ml of a 40% aqueous solution of tetrabutylammonium hydroxide was stirred at room temperature, under N_2, for 25 min. The organic phase was washed with 10% NaOH solution and water and dried over Na_2SO_4. After removal of solvent, the residue was distilled at 52–54 °C (5.5 mm) to give 61.5 g of 1,3-dibromopropane and at 117–120 °C (1.5 mm) to give 34.6 g (75%) of 3-bromopropyl phenyl sulfide.[18] 4-Bromobutyl phenyl sulfide[18] (bp 112–114 °C at 0.6 mm) was prepared similarly in 76% yield.

Preparation of Octyl Phenyl Sulfide by the Coupling of Grignard Reagents and Bromoalkanes. To a Grignard solution, 1.1 equiv, prepared from 906 mg of bromopentane and 144 mg of Mg in 10 ml of THF, under N_2, and at 0 °C, was added 1 ml of a 0.1 M solution of Li_2CuCl_4[12] and 1.26 g of 3-bromopropyl phenyl sulfide, prepared as above, in 5 ml of THF. After stirring for 2 h at 0 °C and 4 h at room temperature, the mixture was poured into water and extracted with ether. The organic phase was washed with water, 5% NaOH solution, and water and dried over Na_2SO_4. Removal of solvent gave 1.23 g of residue which was carefully chromatographed on 50 g of silica gel. Elution with petroleum ether gave 902 mg (87%, based on unrecovered starting material) of octyl phenyl sulfide[14] and 186 mg of 3-bromopropyl phenyl sulfide. The same product was prepared in 70% yield by a similar coupling reaction between 4-bromobutyl phenyl sulfide and butylmagnesium bromide. Alternately, but less conveniently because of a more complex product mixture, the sulfide could be prepared by the coupling of 3-bromomagnesiopropyl phenyl sulfide and bromopentane.

Acknowledgment. We wish to thank CNPq and CAPES for partial support of this work.

Registry No.—Thiophenol, 108-98-5; 1,3-propanedithiol, 109-80-8; 2-phenyl-1-chloroethyl phenyl sulfide, 59092-73-8; 1,3-dibromopropane, 109-64-8; 3-bromopropyl phenyl sulfide, 3238-98-0; 4-bromobutyl phenyl sulfide, 17742-54-0.

References and Notes

(1) R. M. Kellog, *Methods Free-Radical Chem.*, **2**, 1–120 (1969); F. W. Stacey and J. F. Harris, Jr., *Org. React.*, **13**, 150 (1963).
(2) D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969); L. A. Paquette et al., *J. Am. Chem. Soc.*, **93**, 4508 (1971); and references cited therein.
(3) Chloro sulfides have been hydrolyzed to aromatic aldehydes previously,[4] but the yields were only moderate, except in sterically favorable cases, since the resulting thiophenol reacted with the chloro sulfide or aldehyde to form thioacetals as important by-products.[5,6]
(4) H. Gross and G. Matthey, *Chem. Ber.*, **97**, 2606 (1964); P. G. Gassman and D. R. Amick, *Tetrahedron Lett.*, 3466 (1974).
(5) Two publications of a complementary nature appeared after the completion of our work: A. J. Mura, Jr., D. A. Bennett, and T. Cohen, *Tetrahedron Lett.*, 4433 (1975); A. J. Mura, Jr., G. Majetich, P. A. Grieco, and T. Cohen, *ibid.*, 4437 (1975).
(6) Aromatic glyoxals and glyoxal derivatives have been prepared from Pummerer rearrangement products under conditions similar to ours, but the starting materials were β-keto sulfoxides: G. A. Russell and J. Mikol, *J. Am. Chem. Soc.*, **88**, 5498 (1966); G. A. Russell and L. A. Ochrymowycz, *J. Org. Chem.*, **34**, 3618 (1969).
(7) This is essentially an adaptation of Mukaiyama's method for thioketal and thioacetal hydrolysis: K. Marasaka, T. Sakashita, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **45**, 3724 (1972).
(8) The chloro sulfides were formed in near-quantitative yields (NMR).
(9) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
(10) The corresponding oxygen analogue, 3-phenoxypropyl bromide, reacts rapidly with magnesium in ether to give cyclopropane. Phenylmagnesium bromide in the presence of iron or cobalt salts reacts with 3-phenoxypropyl bromide to give a mixture of cyclopropane and propylene: L. H. Slaugh, *J. Am. Chem. Soc.*, **83**, 2734 (1961); M. S. Kharasch, M. Weiner, W. Nudenberg, A. Bhattacharya, T.-I Wang, and N. C. Yang, *ibid.*, **83**, 3232 (1961).
(11) For references to other functional homologation sequences see L. Friedman and A. Shani, *J. Am. Chem. Soc.*, **96**, 7101 (1974); M. Larcheveque and T. Cuvigny, *Tetrahedron Lett.*, 3851 (1975); J. C. Stowell, *J. Org. Chem.*, **41**, 560 (1976); and references cited therein.
(12) M. Tamura and J. K. Kochi, *Synthesis*, 303 (1971).
(13) The latter transformation, together with the sequences described above, for the preparation of dithianes formally illustrate a $^+CH_2(CH_2)_n$–C(=O)–R equivalent, while the reverse illustrates a $^-CH_2(CH_2)_n$–C(=O)–R equivalent.
(14) G. Rabilloud, *Bull. Soc. Chim. Fr.*, 384 (1967).
(15) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971).
(16) C. D. Hurd and L. L. Gershbein, *J. Am. Chem. Soc.*, **69**, 2328 (1947).
(17) T. H. Jones and P. J. Kropp, *Synth. Commun.*, **4**, 331 (1974).
(18) Y. Yano and S. Oae, *Tetrahedron*, **26**, 67 (1970).

Formation of Thioacetals from Sulfoxides under Pummerer-Type Conditions

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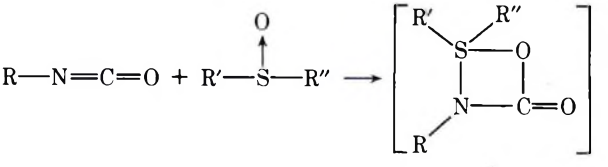
The reaction of isocyanates with sulfoxides has been reported to yield carbon dioxide and sulfilimine derivatives (**2**), presumably via a cyclic intermediate **1**.[1,2] By analogy we anticipated that reaction of sulfoxides with ketenes might lead to **3**. However, when dibenzyl sulfoxide (**4a**) was treated with



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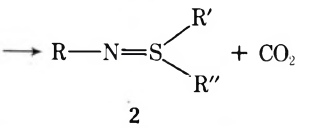

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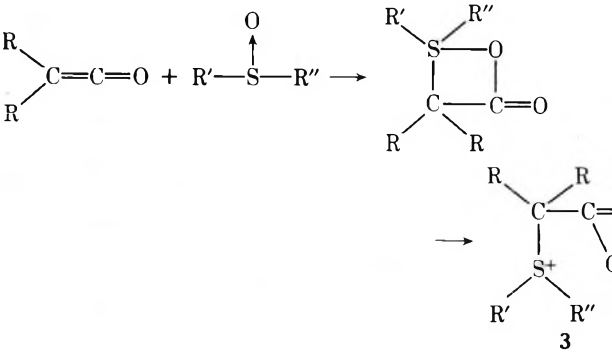


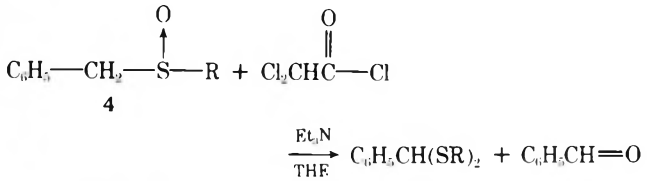
3

Table I. Reaction of Sulfoxides with Acid Chlorides and Anhydrides[i]

Sulfoxide	Acid halide or acid anhydride	Products[a] (% yield[b])
$(C_6H_5CH_2)_2SO$ (4a) (621-08-9)	$CHCl_2COCl$ (79-36-7)	$C_6H_5CH(SCH_2C_6H_5)_2$ (91) (5418-20-2)
4a	$(C_6H_5)_2CHCOCl$ (1871-76-7)	$C_6H_5CH(SCH_2C_6H_5)_2$ (27.4)
4a	AcCl (75-36-5)	$C_6H_5CH(SCH_2C_6H_5)_2$ (5.4); $(C_6H_5CH_2)_2S$ (88)[h] (538-74-9)
4a	Ac_2O[c] (108-24-7)	$C_6H_5CH(SCH_2C_6H_5)_2$ (55.5); $(C_6H_5CH_2)_2S$ (4); $C_6H_5CH_2SCCH_3$ (6.9) (32362-99-5)
4a	$(CHCl_2CO)_2O$[d] (4124-30-5)	$C_6H_5CH(SCH_2C_6H_5)_2$ (76); $(C_6H_5CH_2)_2S$ (21)
$C_6H_5CH_2SC_6H_5$ (4b) (833-82-9)	$CHCl_2COCl$	$C_6H_5CH(SC_6H_5)_2$ (38) (7695-69-4); $C_6H_5CH_2SC_6H_5$ (18) (831-91-4); $C_6H_5CHClSC_6H_5$ (16.5) (21128-89-2)
4b	Ac_2O[e]	$C_6H_5CH(SC_6H_5)_2$ (80) (7695-69-4)
$C_6H_5SCH_3$ (1193-82-4)	$CHCl_2COCl$[d]	$CH_2(SC_6H_5)_2$[f] (11.8) (3561-67-9); $(C_6H_5S)_2$ (3) (882-33-7)
$C_6H_5SCH_3$ (1193-82-4)	Ac_2O[c]	$C_6H_5SCH_2OCCH_3$ (73) (57440-42-3)
$C_6H_5SCH_3$ (1193-82-4)	$(CHCl_2CO)_2O$[d]	$C_6H_5SCH_2OCCHCl_2$[g] (58.5) (59231-04-8)

[a] Known compounds exhibited physical and spectral parameters in agreement with those of authentic samples. [b] Isolated yield after chromatography. [c] Neat in acetic anhydride, 20 h at 100 °C. [d] Anhydrous THF, 1 equiv of dichloroacetic anhydride, 2 h at 25 °C. [e] Anhydrous *p*-xylene, 12 mmol of acetic anhydride, sealed tube at 140 °C for 6 h. [f] Oil, NMR δ 7.50–7.13 (m, 10), 4.31 (s, 2). Anal. Calcd for $C_{13}H_{12}S_2$: C, 67.20; H, 5.21. Found: C, 67.33; H, 5.28. See ref 10. [g] Anal. Calcd for $C_9H_8N_2O_2S_1$: C, 43.04; H, 3.21. Found: C, 43.10; H, 3.31. [h] The conversion of sulfoxides to sulfides on reaction with acid chlorides is a well-known reaction.[11] [i] Registry no. are in parentheses.

dichloroacetyl chloride in tetrahydrofuran containing triethylamine, the usual conditions for generating dichloroketene in situ, the products were benzaldehyde and the dibenzylmercaptal of benzaldehyde **5a** (91% yield). Although the first

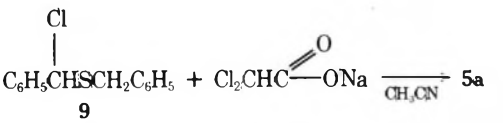


a, R = $CH_2C_6H_5$
b, R = C_6H_5

step in the reaction, under the conditions employed, quite probably is the reaction of the acid chloride with the sulfoxide, the surprising fact is the formation of the mercaptal in high yield rather than the expected α-acyloxy sulfide.

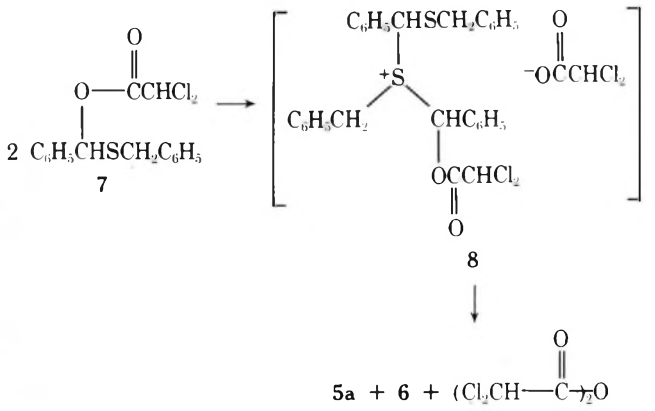
Under the definition suggested by Johnson[3] that the Pummerer reaction embraces a class of reactions involving reduction of a sulfonium sulfur with concomitant oxidation of the α carbon, the above transformation belongs in the broad category of Pummerer reactions. The more usual Pummerer reaction is that of a sulfoxide with a carboxylic anhydride to give an α-acyloxy sulfide[4,5] or α,β-unsaturated sulfides.[6,7] This suggested the possibility that the dibenzylmercaptal of benzaldehyde (**5a**) might be a transformation product of the initially formed α-acyloxy sulfide **7**. In Scheme I a possible mechanism for the conversion of **7** to **5a** is presented. This reaction pathway is analogous to that proposed by Vedejs and Mullins to account for the formation of thioacetal during the thermal rearrangement of a trimethylsilyl sulfoxide.[8]

The key step in the mechanism proposed in Scheme I is the spontaneous reaction of **7** with itself, via an SN1 or SN2 pathway, to give **8**. Subsequent attack on **8** by dichloroacetate anion would then give dichloroacetic anhydride, benzaldehyde (**6**), and the dibenzylmercaptal of benzaldehyde (**5a**). To test the question of whether **7** is stable or whether it would spontaneously undergo conversion to the thioacetal **5a**, an independent synthesis of **7**, involving quite different reaction conditions, was investigated. Treatment of α-chlorobenzyl



benzyl sulfide (**9**) with sodium dichloracetate in anhydrous acetonitrile, which would be expected to give **7** directly, was found instead to produce the dibenzylmercaptal of benzaldehyde (**5a**) in 70% yield. This result provides good evidence for the intermediacy of α-acyloxy sulfide **7** in the formation

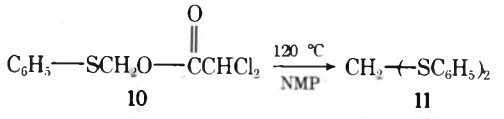
Scheme I



of **5a** and is supportive of the mechanism proposed in Scheme I.

If an α-acyloxy sulfide is first formed during the reaction of a sulfoxide with an acid anhydride or an acid chloride, the question of whether the α-acyloxy sulfide survives intact or is converted to the corresponding thioacetal would be expected to be governed by the usual factors affecting rates of SN1–SN2 reactions. Thus, the nature of the substituents in the sulfoxide as well as the stability of the departing acyloxy anion should play a role. We have carried out several experiments to gain insight regarding these factors and the results are summarized in Table I.

Thus, the reaction of benzyl phenyl sulfoxide (**4b**) with dichloroacetyl chloride under the same conditions as before gave mainly the diphenylmercaptal of benzaldehyde (**5b**) as would be expected. Although methyl phenyl sulfoxide, which lacks benzylic activation, was converted by dichloroacetyl chloride to the corresponding diphenylmercaptal of formaldehyde, the yield was quite poor. Furthermore, the reaction of methyl phenyl sulfoxide with either acetic anhydride or dichloroactic anhydride gave the corresponding α-acyloxy sulfides in good yield. In these instances the reaction conditions were not sufficiently severe for the further conversion of the α-acyloxy sulfides to the acetals. However, when the product, dichloroacetoxymethyl phenyl sulfide (**10**), was heated in *N*-methylpyrrolidone (NMP) at 120 °C for 48 h, it was converted to the diphenylmercaptal of formaldehyde (**11**) in 45% yield.



From these studies it can be concluded that the reaction of sulfoxides with acid halides or acid anhydrides may yield either α-acyloxy sulfides or thioacetals, depending upon the substituents present and the nature of the acid halide or acid anhydride.

Experimental Section

General. Infrared spectra were recorded on a Beckman IR7 spectrophotometer. Solids were recorded as KBr pellets whereas liquids were recorded as thin films on NaCl plates. NMR spectra were recorded on a Varian XL-100 spectrometer using $CDCl_3$ as solvent. Elemental analyses were obtained with a Perkin-Elmer Model 240 C, H, N analyzer. Mass spectra were recorded on a CEC 21-110B mass spectrometer. Melting points were taken with a Dreschel melting point apparatus and are uncorrected. Boiling points were obtained using a micro boiling point tube and are uncorrected. All preparative layer chromatography was done on Analtech silica gel plates.

General Procedure for Reaction of Sulfoxides with Acid Chlorides. A solution of 2 mmol of sulfoxide in 25 ml of anhydrous THF at 25 °C was treated with an equimolar amount of acid chloride. After 15 min 1 equiv of triethylamine was added. The reaction mixture was stirred overnight at 25 °C and the triethylamine hydrochloride was removed by filtration. Concentration of the filtrate under reduced pressure gave an oil which was purified by chromatography.

General Procedure for Reaction of Sulfoxides with Acid Anhydrides. A solution of 2 mmol of sulfoxide in 10 ml of solvent was allowed to react with the appropriate acid anhydride. After completion of the reaction the solution was concentrated under reduced pressure and the resulting oil was purified by chromatography. For specific experimental details see the footnotes of Table I.

Reaction of α-Chlorobenzyl Benzyl Sulfide (9) with Sodium Dichloroacetate. A solution of 0.46 g (2 mmol) of dibenzyl sulfoxide (**4a**) in 10 ml of anhydrous CH_2Cl_2 was added dropwise over a 30-min period to a refluxing solution of 0.17 ml (15% excess) of thionyl chloride in 20 ml of anhydrous CH_2Cl_2. The solution was refluxed for 3 h and concentrated under reduced pressure to give **9** as a slightly yellow oil. A solution of **9** in anhydrous acetonitrile was treated with 0.30 g (2 mmol) of sodium dichloroacetate. A milky precipitate formed immediately. The mixture was stirred for 3 days at 25 °C, the precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure to give a viscous oil. Preparative layer chromatography gave 235 mg (70%) of the dibenzylmercaptal of benzaldehyde (**5a**), mp 59–61 °C (lit.[9] mp 61 °C).

Pyrolysis of Dichloroacetylmethyl Phenyl Sulfide (10). A solution of 120 mg (0.48 mmol) of **10** in 1 ml of anhydrous oxygen-free *N*-methylpyrrolidinone was heated at 120 °C for 48 h. The solution was diluted with 25 ml of $CHCl_3$ and washed with three 15-ml portions of H_2O. The solution was dried•($MgSO_4$) and concentrated under reduced pressure to give a dark oil. Preparative layer chromatography gave 25 mg (45%) of the diphenylmercaptal of formaldehyde (**11**).

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Registry No.—**9**, 51317-73-8; thionyl chloride, 7719-09-7; sodium dichloroacetate, 2156-56-1.

References and Notes

(1) C. King, *J. Org. Chem.*, **25**, 352 (1960).
(2) G. Schulz and G. Kresze, *Angew. Chem.*, **75**, 1022 (1963).
(3) C. R. Johnson and W. G. Phillips, *J. Am. Chem. Soc.*, **91**, 682 (1969).
(4) L. Horner, *Justus Liebigs Ann. Chem.*, **631**, 198 (1960).
(5) L. Horner and P. Kaiser, *Justus Liebigs Ann. Chem.*, **626**, 19 (1959).
(6) W. E. Parham and R. Koncos, *J. Am. Chem. Soc.*, **83**, 4034 (1961).
(7) W. E. Parham et al., *J. Org. Chem.*, **29**, 2211 (1964).
(8) E. Vedejs and M. Mullins, *Tetrahedron Lett.*, 2017 (1975).
(9) R. J. Kern, *J. Am. Chem. Soc.*, **75**, 1865 (1953).
(10) H. S. Struck and W. J. Jorison, *J. Am. Chem. Soc.*, **52**, 2060 (1930).
(11) T. Numata and S. Oae, *Chem. Ind. (London)*, 277 (1973).

Cuprous Chloride Catalyzed Alkylations of β Diketones with Methylene Halides

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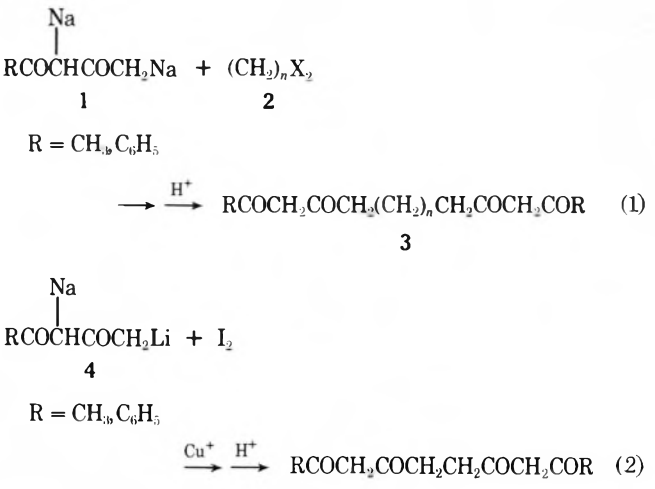
It has been observed previously that α,ω dihaloalkanes will alkylate dianions of β diketones to form bis-β diketones (eq 1) where $n = 3$ or higher. However, it was also observed that the alkylation reaction did not work for $n = 1$ or 2 under the same conditions.[1] We have recently found that cuprous ions can catalyze coupling reaction of dianions of β diketones that do not readily occur under the conditions or with reagents

usually used for coupling in the absence of cuprous ions (eq 2).[2]



$$\underset{\mathbf{1}}{RCOCHCOCH_2Na} + \underset{\mathbf{2}}{(CH_2)_nX_2}$$

$R = CH_3, C_6H_5$

$$\xrightarrow{H^+} RCOCH_2COCH_2(CH_2)_nCH_2COCH_2COR \quad (1)$$

$$\underset{\mathbf{3}}{}$$

$$\underset{\mathbf{4}}{RCOCHCOCH_2Li} + I_2$$

$R = CH_3, C_6H_5$

$$\xrightarrow{Cu^+}\xrightarrow{H^+} RCOCH_2COCH_2CH_2COCH_2COR \quad (2)$$

We now report that sodiolithio-2,4-pentanedione (**4**, R = CH_3) reacts with methylene and ethylene bromide (**2**, n = 1 and 2, respectively) to form the alkylation products **3**. These products were not obtained when the reaction was run under the same conditions in the absence of the copper catalyst. When dibromomethane was used (−63 to 0 °C, 3 h) as the substrate, 2,4,8,10-undecanetetrone was isolated in 8–10% yields. The low yield could be attributed to unreacted starting material (observed by gas chromatography) and intramolecular condensation of the alkylation product.[3] When diiodomethane was used as the substrate, a tar was formed from which the bis-β diketone **3** could not be isolated nor could starting material be detected by gas chromatography.

When 1,2-dibromoethane (**2**, n = 2) was used as substrate with **1** in the presence of cuprous ions 2,4,9,11-dodecanetetrone was isolated as a solid in 25–33% yield. The somewhat low yield of the bis-β diketone may be caused by incomplete crystallization of the low-melting product or intramolecular condensation side reactions[3] since ethylene bromide was shown to be absent from the crude reaction product. When 1,2-dichlorethane was used as the substrate, 2,4-pentanedione and 1,2-dichlorethane were recovered in 52 and 33% yields, respectively. This suggests that E_2 elimination may be the main reaction as in the reaction between disodio-2,4-pentanedione and ethylene chloride in liquid ammonia.[1] This difference in alkylation reactivity of bromo compounds vs. chloro compounds is consistent with previous observations of reactions of some haloacetals[4] and halocarboxylates[5] with dianions of β diketones.

That the alkylation products from these reactions are **3**, n = 1 and 2, respectively, is supported by analogy with homologues, ir and ^1H NMR spectra, and elemental analysis (see Experimental Section).

Experimental Section

Melting points were determined using capillary tubes in a Thomas-Hoover melting point apparatus. Infrared spectra were obtained with a Perkin-Elmer 257 grating infrared spectrophotometer using KBr pellets. The ^1H NMR spectra were obtained using a Varian Model A-60D spectrometer and samples dissolved in CCl_4 with Me_4Si as internal standard.

Condensation of Dibromomethane with 4. The sodiolithio-2,4-pentanedione (0.05 mol)–cuprous chloride (0.0076 mol) reagent was prepared in the THF as described previously.[2] To this mixture at −63 °C under an argon atmosphere was added a solution of 4.4 g (0.025 mol) of dibromomethane in 15 ml of THF over 15 min. After the mixture had stirred for 3 h, the reaction mixture was allowed to warm to 0 °C. It was quenched with ice and acidified with cold concentrated hydrochloric acid. The aqueous phase was extracted three times with 25 ml of ether. The ethereal solution was washed once with 30 ml of saturated sodium chloride solution and dried over anhydrous sodium sulfate.

Removal of solvent afforded about 8.0 g of a green, viscous liquid containing 2,4-pentanedione and dibromomethane as major components (VPC analysis). It was triturated in absolute ethanol and petroleum ether (bp 35–60 °C) and cooled in liquid nitrogen to afford 8–10% of 2,4,8,10-undecanetetrone as a light yellow solid, mp 59–60 °C. The solid was enolic to ferric chloride solution (red-brown color): ir (CCl_4) 2980, 2950, 1730, 1710 (m), 1680 cm^{-1}; ^1H NMR (CCl_4) τ 8.0 (s, 6 H) O=CCH$_3$, 7.4–7.85 (m, 6 H) O=CCH$_2$CH$_2$CH$_2$C=O, 4.55 (s, 2 H) -CH=C, and −4.50 (broad hump, 2 H) -C=COH. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.27; H, 7.55. Found: C, 62.18; H, 7.46.

The reaction was repeated using diiodomethane. A yellow, viscous liquid (4.8 g) was obtained. VPC analysis showed the absence of 2,4-pentanedione and diiodomethane. No **3**, n = 1, could be isolated from the liquid.

Condensation of 1,2-Dibromoethane with 4. To the sodiolithio-2,4-pentanedione–cuprous chloride reagent at −5 °C under a nitrogen atmosphere was added a solution of 4.7 g (0.025 mol) of 1,2-dibromomethane in 20 ml of dry THF over 15–20 min. The resulting yellowish-brown mixture was stirred for 8 h while the temperature slowly rose to 25 °C. The workup procedure described above afforded 4.0 g of a yellowish-green syrup. The liquid was dissolved in absolute ethanol and cooled in a freezer to obtain 1.4–1.8 g (25–33%) of 2,4,9,11-dodecanetetrone as a pale yellow solid, mp 48–52 °C. The compound gave a red-brown coloration with ferric chloride solutions. Recrystallization from absolute ethanol and vacuum drying gave an analytical sample: mp 52–53 °C; ir (CCl_4) 2960, 2930, 2860, 1715, 1680–1550 (broad), 1460, 1430, 1360, 1235, 1130, 1000 cm^{-1}; ^1H NMR (CCl_4) τ 8.3 (m, 4 H), 8.0 (s, 6 H), 7.7 (m, 4 H), 7.4 (s, ~1.5 H), 4.64 (s, ~2 H), −5.0 (hump, ~2 H).[6] Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 64.17; H, 8.17.

The reaction was repeated using 1,2-dichloroethane. This afforded 8.0 g of a liquid which showed starting materials by VPC. Fractional distillation gave 2.6 g (52%) of 2,4-pentanedione and 0.8 g (33%) of ethylene chloride and about 2.4 g of intractable pot residue.

Registry No.—**3** (R = CH_3; n = 1), 58816-10-7; **3** (R = CH_3; n = 2), 58816-11-8; **4** (R = CH_3), 56580-16-6; cuprous chloride, 7758-89-6; dibromomethane, 74-95-3; 2,4-pentanedione, 123-54-6; 1,2-dibromoethane, 106-93-4; 1,2-dichloroethane, 107-06-2; diiodomethane, 75-11-6.

References and Notes

(1) K. G. Hampton, R. J. Light, and C. R. Hauser, *J. Org. Chem.*, **30**, 1413 (1965).
(2) K. G. Hampton and J. J. Christie, *J. Org. Chem.*, **40**, 3887 (1975).
(3) L. Weiler and S. H. Huskin, *J. Am. Chem. Soc.*, **96**, 1082 (1974).
(4) K. G. Hampton and R. E. Flannery, *J. Chem. Soc., Perkin Trans. 1*, 2308 (1973).
(5) R. O. Pendarvis and K. G. Hampton, *J. Org. Chem.*, **39**, 2289 (1974).
(6) NMR spectra of β diketones are complicated by extensive keto–enol tautomerism. It is observed that the absorptions may not be of integral intensity in this series of compounds because of this phenomenon.

A Facile Synthesis of (+)-Pinol from (−)-Carvone

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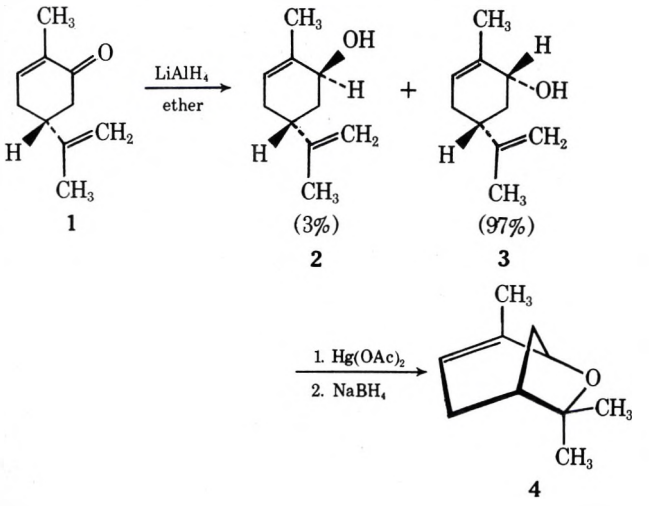
The use of chiral solvents in the determination of optical purity, particularly in the presence of lanthanide shift reagents, has received a great deal of recent attention.[1] In our studies of synthetic schemes leading to chiral solvents, we have developed a new and convenient route to the chiral bicyclic ether, (+)-pinol[2,3] (**4**), by the use of the oxymercuration–demercuration reaction. The route involves the stereospecific reduction of (−)-carvone with lithium aluminum hydride to

give (−)-*cis*-carveol (**3**). This is followed by internal oxymercuration with mercuric acetate and reduction with sodium borohydride to give the bicyclic ether in 83% overall yield.[4]



1 2 3 4

Reduction of (−)-carvone (**1**) with $LiAlH_4$ in ether at room temperature yields a mixture of *trans*- and *cis*-carveols.[5] Lowering the reaction temperature to −78 °C provides a near-quantitative yield of the alcohol containing 97% of the isomer with the desired cis stereochemistry. The alcohol isolated from the reduction was of adequate purity to be used directly in the next step.

Halpern and Tinker[6] have observed that the second-order rate constant for the intramolecular oxymercuration of 1-penten-5-ol to form the cyclic product is more than 10 times greater than the corresponding oxymercuration of 1-butene. This result is explained by the neighboring group participation of the terminal hydroxy group. Treatment of (−)-*cis*-carveol with an equimolar amount of mercuric acetate in a tetrahydrofuran–water mixture provided, after 9 days, greater than 85% conversion to the ring-closed mercurial, **5**, as shown by gas chromatography. The observation that only the (−)-*cis*-carveol undergoes internal oxymercuration and the (−)-*trans*-carveol fails to react provides direct and conclusive proof for the stereochemistry of the carveols.[5b]

Reduction of the mercurial was readily accomplished with sodium borohydride in an aqueous solution containing 0.4 M NaOH. Attempts to reduce the mercurial under less basic conditions or through the use of weaker reducing agents ($NaBH_3CN$) resulted in low yields of **4** with the major fraction of the mercurial reverting to the (−)-*cis*-carveol. This result is presumably due to the acid-promoted deoxymercuration of **5** to form **3** and Hg^{2+} followed by reduction of the Hg^{2+} by borohydride. Deoxymercuration is generally facile in the presence of coordinating anions such as acetate ion.[7] The results further suggest that the rate of reduction of Hg^{2+} is more rapid than the rate of reduction of **5**. Hence, by slowing down the deoxymercuration reaction that forms Hg^{2+} the pathway leading to the reduction of the alkyl mercurial will favorably compete with the pathway leading to the reduction of Hg^{2+}.

Experimental Section

Gas chromatographic analyses were carried out on a Varian Series 1200 gas chromatograph fitted with a 10-ft 3% Carbowax 20M column and temperature programmed from 120 to 170 °C at 10 °C/min. Optical rotations were measured on a Perkin-Elmer 114 polarimeter using 5-ml cells. Refractive indices were determined with a Bausch and Lomb refractometer.

(−)-*cis*-Carveol (3). To 12.0 g (0.316 mol) of $LiAlH_4$ (Alpha Inorganics) in 700 ml of anhydrous diethyl ether cooled to −78 °C was added dropwise 46.6 g (0.310 mol) of (−)-carvone (Aldrich) in 75 ml of anhydrous diethyl ether over a 1-h period. Aliquots were removed, quenched with aqueous H_2SO_4, and the ether layer analyzed directly with gas chromatography. After an additional 30 min, the reduction was complete and the excess $LiAlH_4$ was quenched with a solution of wet ether. This mixture was then poured onto crushed ice; 200 ml of 10% H_2SO_4 was added, and the ether and aqueous layers were separated. The aqueous layer was extracted with two additional 100-ml portions of ether. All the ether layers were combined and dried over anhydrous sodium sulfate, and the solvent was removed in vacuo to yield 46.1 g (97.7%) of a clear liquid containing 97% (−)-*cis*-carveol and 3% (−)-*trans*-carveol. The (−)-carveol mixture obtained was used in the next step without further purification: bp 110 °C (13 mm); $[\alpha]^{25}D$ −25.8° (neat); $n^{25}D$ 1.4960 [lit.[5] bp 101 °C (10 mm); $[\alpha]^{25}D$ −23.9° (neat); $n^{25}D$ 1.4959]. Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.57; H, 10.60.

(+)-Pinol (4). To a solution of 15.25 g (0.100 mol) of (−)-carveol mixture in 100 ml of THF was added dropwise a solution consisting of 30.60 g (0.096 mol) of mercuric acetate in 50 ml of water. The progress of the reaction was monitored by gas chromatography. Reaction aliquots were removed periodically and quenched with base and reduced by the addition of 0.5 M $NaBH_4$ in 3 M NaOH; the aqueous phase was saturated with sodium chloride, and the THF phase analyzed directly with gas chromatography. The results indicated that more than 85% of the (−)-carveol mixture was converted to the oxymercurated product after 9 days.

The solution containing the oxymercurated product was cooled to 15 °C and made basic with the dropwise addition of 25 ml of 3 M NaOH. A cooled solution consisting of 5.7 g (0.15 mol) of sodium borohydride (Alpha Inorganics) and 100 ml of 3 M NaOH was then added dropwise to the basic solution of the mercurial. After a 3-h reaction period the aqueous phase was saturated with NaCl and 25 ml of ether was added to aid in the separation of phases. The organic phase was removed and dried over anhydrous sodium sulfate. The THF–ether in the organic phase was removed by distillation at atmospheric pressure. Two distillations of the crude product under reduced pressure provided **4** in greater than 99% purity: bp 65 °C (11 mm); $[\alpha]^{25}D$ 81.1° (neat); $n^{25}D$ 1.4670 [lit.[2] bp 64–65 °C (11 mm); $[\alpha]^{25}D$ 87.5°; $n^{20}D$ 1.4698]; NMR (neat) δ 4.98 (m, 1), 3.75 (d, 1, J = 3.5 Hz), 1.50–2.28 (m, 8), 1.19 (s, 3), 1.08 (s, 3). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.57; H, 10.47.

Registry No.—**1**, 6485-40-1; **2**, 2102-58-1; **3**, 2102-59-2; **4**, 55822-06-5.

References and Notes

(1) See, for instance, C. P. Jennison and D. Mackay, *Can. J. Chem.*, **51**, 3726 (1973); W. Pirkle, S. D. Beare, M. Kainosho, and K. Ajiska, *J. Am. Chem. Soc.*, **94**, 5924, (1972), and references cited therein.
(2) R. Lombard and G. Heywang, *Bull. Soc. Chim. Fr.*, 1210 (1954), and references cited therein.
(3) (+)-4,7,7-Trimethyl-6-oxabicyclo[3.2.1]oct-3-ene.
(4) Previous synthesis (see ref 2) starting from α-terpenol only provided about a 30% yield of (+)-pinol.
(5) (a) D. Lloyd and J. Read, *Chem. Ind. (London)*, 436 (1953); (b) S. H. Schroeter and E. L. Eliel, *J. Org. Chem.*, **30**, 1 (1965); (c) R. H. Reitsema, *J. Am. Chem. Soc.*, **75**, 1996 (1953); (d) R. G. Johnston and J. Read, *J. Chem. Soc.*, 233 (1934).
(6) J. Halpern and H. B. Tinker, *J. Am. Chem. Soc.*, **89**, 6427 (1967).
(7) W. Kitching, *Organomet. Chem. Rev.*, **3**, 61 (1968).

Non-Saytzeff Alumina-Catalyzed Dehydration of 2-Ferrocenyl-3-methyl-2-butanol

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In the last 10 years a wide investigation on the heterogeneous dehydration of alcohols catalyzed by metal oxides gave some explanations on how the metal oxide works as a catalyst. The results are reviewed in the literature.[1-4]

As to orientation, alumina,[5,6] hydroxyapatite,[7] and thoria[8] have been found to be very selective with respect to elimination from secondary alcohols. Alumina and hydroxyapatite

give predominant Saytzeff orientation, while with thorium oxide Hofmann orientation is found. The sole exception is that reported by Vojtko et al.,[9] who obtained 97% of $Me_2CHCH_2CH{=}CH_2$ from the dehydration of 4-methyl-2-pentanol over alumina at 250 °C.

More recently, other Lewis acids, such as nickel sulfate, aluminum sulfate, zinc sulfide, and silica, have been used as catalyst in the dehydration of secondary alcohols,[10] the resulting orientation being analogous to that observed with alumina.

Fewer studies regard tertiary alcohols, but no selectivity is found with both alumina and thoria, as the Saytzeff/Hofmann ratio is a statistical one, depending on the number of hydrogens.

Also, the recent result reported by Peeters[11] about a non-Saytzeff dehydration of 2-methyl-2-pentanol over Al_2O_3 falls actually within the general behavior. This author obtains 65.3 as the highest percentage of 1-alkene, with a value of 70% after extrapolating to zero contact time, in order to neglect isomerization. With this alcohol the statistical orientation would give 75% of the terminal olefin.

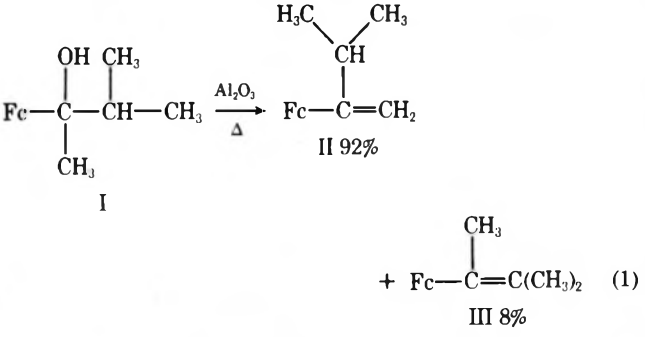
We now wish to report a truly non-Saytzeff result as obtained by the dehydration of 2-ferrocenyl-3-methyl-2-butanol (I) over Al_2O_3.

Ferrocenyl alcohols are known to undergo dehydration when treated with alumina.[12-14]

In the course of our studies on the methoxymercuration of vinylferrocene and related compounds,[15] the alkenes have been prepared by heating a mixture of alumina and the appropriate alcohol without solvent by a modification of the methods reported in the literature.[12-14]

After 2-ferrocenyl-3-methyl-2-butanol (I) was heated with Al_2O_3, the reaction mixture was taken up on a column and eluted with 40–70 °C petroleum ether to yield a red oil. On VPC examination this product was shown to consist of two species in the ratio 9:1. The NMR spectrum of the mixture in CCl_4 solution, Me_4Si being the internal standard, shows a group of signals which can be attributed to α-isopropylvinylferrocene (II) as follows: δ 1.17, doublet, J = 7 Hz, and δ 2.67, septet, J = 7 Hz (area ratio 6:1), due to the isopropyl group; δ 3.95, singlet, and δ 4.00–4.57, multiplet, due to the ferrocenyl system; δ 5.12 and 4.82, doublets, J = 2 Hz, due to the vinylic β protons.

Two more signals, i.e., at δ 1.72 and 2.02, with relative intensities 2:1, can be attributed to α,β,β-trimethylvinylferrocene (III). By comparing the areas of these signals with those due to the isopropyl protons, the more alkylated olefin turns out to form in 8% yield of the total product (eq 1):



(1)

This result is reproducible and independent of temperature in the tested range (105–180 °C). Contact times were between 10 min and 1 h, the percentage of α,β,β-trimethylvinylferrocene increasing with time up to 15%.

A run at 110 °C was quenched after 1 min to yield isopropylvinylferrocene exclusively.

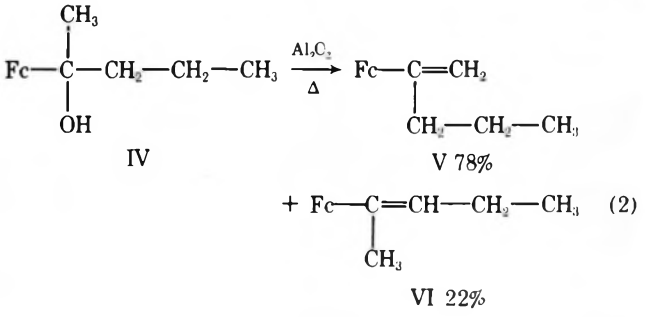
Ca. 1% of III appears when isopropylvinylferrocene is heated for 30 min at 140 °C, thus indicating that isomerization is negligible under the conditions used.

Dehydration experiments were made also with 2-ferrocenyl-2-pentanol (IV) and 2-ferrocenyl-2-butanol (VII), by heating these alcohols with Al_2O_3 for 20 min at 150 °C.

The reaction mixtures, treated as described above and examined on VPC, showed two peaks in both cases, their ratios being 9:1 and 8:1, respectively.

The NMR spectra of these mixtures in CCl_4 solutions are quite complicated in the alkyl protons region. However, it is possible to attribute the signals in the vinyl protons region to the different isomers.

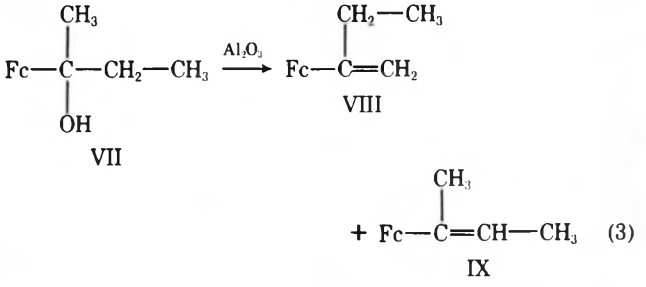
Thus, the dehydration product of 2-ferrocenyl-2-pentanol (IV) (eq 2) shows two doublets at δ 5.48 and 5.08 (J = 2 Hz),



(2)

due to the β vinylic protons of V, and a broad singlet at δ 4.72, due to the β vinylic proton of VI. By comparing the areas of these signals, V and VI turn out to be 78 and 22% of the total amount.

The dehydration product of 2-ferrocenyl-2-butanol (VII) (eq 3) shows two doublets, at δ 5.52 and 5.12 (J = 2 Hz), due



(3)

to the β vinylic protons of VIII, and a broad singlet at δ 4.78, due to the β vinylic proton of IX. By comparing the areas of these signals, VIII and IX turn out to be 85 and 15% of the total amount.

It may be worth noting that the observed orientation does not appear to result from a stability difference due to hindrance to coplanarity in compound III, as compared to II. Judging from Dreiding models, coplanarity of the vinylic double bond with the cyclopentadienyl ring seems equally well attained in both cases. Further work is needed for an assessment of the orientation factors involved under the investigated conditions.

Experimental Section

VPC experiments have been carried out with a Fractovap C Erba instrument equipped with 1-m column of 5% methylsilicone SE-30 on Chromosorb W 60–80 with 0.5% ATPET.

NMR spectra were recorded with a JEOL C60-HL spectrometer, using CCl_4 as solvent and Me_4Si as internal standard.

Alumina (Merck, neutral, Brockmann) sieved to 80–140 mesh was calcined in air at 500 °C[10] and immediately used for the dehydration runs, after cooling under dry nitrogen atmosphere. The same results of dehydration isomer distribution were obtained by using neutral alumina (Merck, Brockmann I) sieved to 140–230 mesh, basic alumina (Merck, Brockmann I) sieved to 140–230 mesh, basic alumina (Merck, Brockmann I) sieved to 80–140 mesh, and commercial neutral alumina (Merck, Brockmann II–III).

2-Ferrocenyl-3-methyl-2-butanol (I) was obtained in a 100% yield by treating 2.6 g (0.01 mol) of isobutyrylferrocene with the equivalent amount of methyllithium in anhydrous diethyl ether. The reaction layer, hydrolyzed with aqueous 10% NH_4Cl, extracted with diethyl ether, and dried over anhydrous Na_2SO_4, gave an orange-yellow solid (mp 43–44 °C), the structure of which was confirmed by NMR spectroscopy.

Isobutyrylferrocene has been prepared in a 69% yield by Friedel–Crafts acylation of ferrocene with isobutyryl chloride and aluminum chloride in CH_2Cl_2.[16]

2-Ferrocenyl-2-pentanol and 2-ferrocenyl-2-butanol were prepared by the same way, starting from butyrylferrocene and propionylferrocene, respectively. These ketones were synthesized according to the literature.[17,18]

Several runs of alumina-catalyzed dehydration have been performed by heating 1 g of 2-ferrocenyl-3-methyl-2-butanol with 50 g of Al_2O_3 without solvent, at a temperature ranging between 105 and 180 °C and reaction times from 10 min to 1 h. The brown reaction mixture was eluted with 40–60 °C petroleum ether on an alumina column. The red oil obtained after evaporation of the solvent was examined by VPC and NMR. Like other vinylferrocenes, the reaction products decompose on standing, both in solution and without solvent, to give a brown residue, which is insoluble in organic solvents.

Acknowledgment. The author wishes to thank Professor G. Illuminati for helpful discussions.

Registry No.—I, 36928-96-8; isobutyrylferrocene, 41406-84-2.

References and Notes

(1) H. Knoezinger, *Angew. Chem., Int. Ed. Engl.*, **7**, 791 (1968).
(2) B. Notari, *Chim. Ind. (Milan)*, **51**, 1200 (1969).
(3) H. Bremer, K. H. Steinberg, J. Glietsch, H. Lusky, U. Werner, and K. D. Weinlandt, *Z. Chem.*, **10**, 161 (1970).
(4) H. Noller, P. Andreu, and M. Hunger, *Angew. Chem., Int. Ed. Engl.*, **10**, 172 (1971).
(5) H. Pines and J. Manassen, *Adv. Catal. Relat. Subj.*, **16**, 49 (1966).
(6) E. J. Blanc and H. Pines, *J. Org. Chem.*, **33**, 2035 (1968).
(7) C. L. Kibby, S. S. Lande, and W. K. Hall, *J. Am. Chem. Soc.*, **94**, 214 (1972).
(8) A. J. Lundeen and R. van Hoozer, *J. Org. Chem.*, **32**, 3386 (1967).
(9) J. Vojtko, M. Hrusovsky, and M. Cihova, *Petrochemia*, **12**, 73 (1972); *Chem. Abstr.*, **78**, 71301v (1973).
(10) T. Yamaguchi and K. Tanabe, *Bull. Chem. Soc. Jpn.*, **47**, 424 (1974).
(11) H. L. Peeters, *J. Chem. Soc., Chem. Commun.*, 1330 (1972).
(12) F. S. Arimoto and A. C. Haven, *J. Am. Chem. Soc.*, **77**, 6295 (1955).
(13) K. Schlögl and A. Mohar, *Monatsh. Chem.*, **92**, 219 (1961).
(14) K. Schlögl and A. Mohar, *Naturwissenschaften*, **9**, 376 (1961).
(15) B. Floris and G. Illuminati, *Coord. Chem. Rev.*, **16**, 107 (1975), and unpublished work.
(16) Modification of the literature method: R. J. Stephenson, British Patent 864 197; *Chem. Abstr.*, **55**, 17647 (1961).
(17) M. D. Rausch and L. E. Coleman, *J. Org. Chem.*, **23**, 107 (1958).
(18) E. L. De Young, *J. Org. Chem.*, **26**, 1312 (1961).

Carbonyl Oxygen Exchange of Phenyl Acetate during Acid-Catalyzed Hydrolysis

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The hydrolysis reactions of carboxylic acid derivatives usually proceed through tetrahedral addition intermediates, whose presence has generally been inferred from the observation of carbonyl oxygen exchange concurrent with the hydrolysis.[1] We report here an investigation into the extent of such exchange during the acid-catalyzed hydrolysis of phenyl acetate. No such study appears to have been reported, although phenyl esters have been found to undergo *no* exchange during base hydrolysis,[2] an observation which can be explained in terms of expulsion of the better leaving group, phenoxide, from the tetrahedral intermediate.

In general the A-2 hydrolysis of phenyl esters is found to be very similar to that of simple alkyl esters, for example in comparisons of absolute rates,[3] entropies of activation,[4] rate–acidity dependencies,[5] and substituent effects.[4–6] Some difference might, however, be anticipated in the exchange process with the quite different leaving group tendencies of *O*-phenyl vs. *O*-alkyl.

Experimental Section

Phenyl Acetate-*carbonyl*-^{18}O. The hydrochloride salt of *O*-phenyl-*N*-methylacetimidate[7] (15 g) was mixed with 30 ml of dry acetonitrile and 2 g of ^{18}O water (12.3% ^{18}O, Miles Laboratories) was added. After refluxing for 1 h, the cooled solution was added to water and extracted with ether. Quantitative GC analysis of the ether extract revealed that the imidate salt had been completely hydrolyzed, but to a mixture of 65% phenyl acetate and 35% phenol. The latter was removed by washing briefly with cold 1 N NaOH. Washing with water, drying ($MgSO_4$), and distillation yielded pure ester, isolated yield 6.4 g (58%). Mass spectrometric analysis indicated an ^{18}O content of ca. 12.2%.

A variety of experimental conditions were employed in an attempt to improve the yield of ester, but in every case lower yields in fact resulted, the remainder of the product being phenol. Hydrolysis in 0.1 N HCl was found to produce 66% phenyl acetate and 34% phenol. (Under the hydrolysis conditions the ester product is stable.)

Hydrolysis. The hydrolysis rate in 1.5 N HCl in 40:60 (v/v) dioxane–water was determined as previously described.[5]

Exchange. The labeled ester (2 g) was dissolved in 500 ml of 1.5 N HCl in 40:60 dioxane–H_2O and the solution thermostated at 25.0 °C. At appropriate intervals samples were withdrawn and extracted with methylene chloride. This was washed with cold 1 N NaOH and water and dried ($MgSO_4$) and the solvent was removed. GC analysis showed that the small amount of remaining liquid was pure ester.

The ^{18}O content of this ester was determined by direct mass spectrometric analysis on an AEI MS902 equipped with a vacuumetrics ratiometer. With each sample approximately 40 values of the (P + 2)/P ratio were obtained by repeat scanning, and the average value then was compensated for natural abundance of isotopes in other positions.[8] The reproducibility was about 0.03 atom % for samples run during the same day. In a control experiment a sample of labeled ester was mixed with ca. tenfold of its hydrolysis products, dissolved in the hydrolysis medium, and immediately subjected to the workup and analysis procedure. No change was observed in the amount of label present.

Results and Discussion

The ^{18}O content of unreacted phenyl acetate is listed for varying amounts of hydrolysis in Table I, and plotted as a function of hydrolysis in Figure 1. These reveal a small, but significant amount of exchange concurrent with hydrolysis, and yield a value of 120 for k_H/k_E, the ratio of the hydrolysis and exchange rates.

Table I. Excess Oxygen-18 in Phenyl Acetate Samples after Partial Hydrolysis in Acidic Solution[a]

Completion of hydrolysis,[b] %	% ^{18}O (excess)	
	Run A	Run B
0	11.98	12.07
48.0	11.88	12.00
73.0	11.85	11.94
86.0	11.77	11.87
92.7		11.82
k_H/k_E[c]	118	124

[a] 40:60 dioxane–water containing 1.5 N HCl. [b] Rate constant for hydrolysis = 0.000218 s^{-1}. [c] Reciprocal of slope of plot of log (P/P_0) vs. log ([ester]/[ester]$_0$); see Figure 1.

In comparison to simple alkyl esters this value is considerably larger, e.g., with ethyl acetate[9] and *n*-propyl acetate,[4] $k_H/k_E = 5$, and with methyl formate,[10] $k_h/k_E = 11$. These k_H/k_E ratios are determined by the partitioning of the tetrahedral intermediate to reagents (exchange) or products (hydrolysis), recognizing that in acid solution the breakup of this

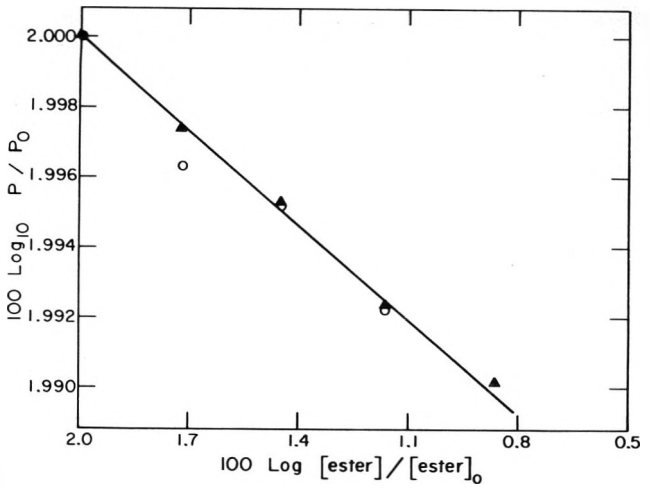
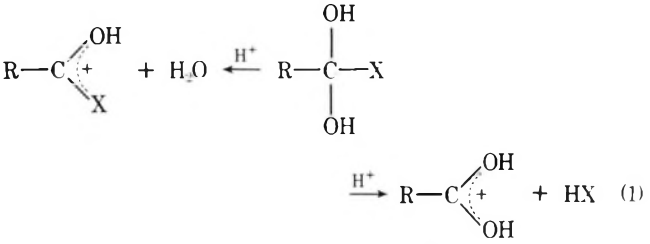


Figure 1. Concurrent hydrolysis and exchange of phenyl acetate; P, P_0 = % ^{18}O (excess) at times t and 0, (○,▲) = duplicate experiments.

intermediate is probably acid catalyzed with expulsion of a neutral leaving group and formation of a resonance stabilized cation, eq 1 (where the proton transfer may occur simulta-



neously with leaving group departure or in a prior equilibrium). Three factors are then important in determining k_H/k_E: (1) the intrinsic leaving group abilities of HX vs. H_2O, (2) the basicities of X vs. OH, and (3) the relative stabilities of the cationic products (i.e., the driving force for expulsion[11]). For phenyl acetate 1 and 3 favor the forward process (expulsion of PhOH) while 2 favors the reverse (expulsion of H_2O), the observed k_H/k_E ratio then suggesting that the former are more important.

This is the opposite situation to that found in considering amide hydrolysis and exchange, where again hydrolysis dominates (e.g., for benzamide, $k_H/k_E = 320$[12]). Here, however, one must argue that factor 2, the much greater basicity of nitrogen, is the more important, since 1 and 3 must favor expulsion of OH over NH_2.

Acknowledgments. The author gratefully acknowledges the financial support of the National Research Council of Canada.

Registry No.—*o*-Phenyl-*N*-methylacetimidate, 22084-79-3; acetonitrile, 75-05-8; phenyl acetate, 122-79-2; phenol, 108-95-2.

References and Notes

(1) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); D. Samuel and B. L. Silver, *Adv. Phys. Org. Chem.*, **3**, 124 (1965).
(2) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956).
(3) A. J. Kirby, "Comprehensive Chemical Kinetics", Vol. 11, C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, Amsterdam, 1972, pp 57–142.
(4) R. A. McClelland, Ph.D. Thesis, University of Toronto, 1969.
(5) K. Yates and R. A. McClelland, *J. Am. Chem. Soc.*, **89**, 2686 (1967).
(6) F. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).
(7) Y. Pocker, M. W. Beug, and K. L. Stephens, *J. Am. Chem. Soc.*, **96**, 1974 (1974).
(8) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds", Wiley, New York, N.Y., 1964, p 20.
(9) C. A. Lane, M. F. Cheung, and G. F. Dorsey, *J. Am. Chem. Soc.*, **90**, 6492 (1968).
(10) C. B. Sawyer and J. F. Kirsch, *J. Am. Chem. Soc.*, **95**, 7375 (1973).
(11) N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 489 (1974).
(12) R. A. McClelland, *J. Am. Chem. Soc.*, **97**, 5281 (1975).

Carbon-13 Nuclear Magnetic Resonance Spectra of Kojic Acid and Other 4-Pyrone Derivatives

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4-Pyrone derivatives are common flavoring agents and food preservatives which have been investigated with regard to bactericidal activity.[1] Considerable uncertainty remains as to the degree of aromaticity of kojic acid and of its parent structure, 4-pyrone, despite the application of a large number of chemical and spectroscopic criteria.[2,3] Thus, 4-pyrones are reported to give substitution products upon bromination.[4] The lack of reactivity of 4-pyrones in Diels–Alder reactions is remarkable.[5] The dipole moment of 4-pyrone (ca. 4 D) is substantially larger than that calculated for a non-resonance-stabilized molecule (ca. 2 D).[3,6,7]

The ^1H NMR spectra have been interpreted in terms of ring current effects, which were considered to reflect a high degree of aromaticity.[6] Abraham has questioned deductions regarding the degree of aromaticity based on ring current effects,[8] and these observations remain controversial. The vicinal ^1H coupling constant between H-2 and H-3 (5.9 or 6.2 Hz)[3,9] is similar both to aromatic compounds and to 2-cyclohexenone.

The most damaging evidence against aromaticity is the very low magnetic susceptibility, which is regarded by Beak et al. as indicative of essentially no aromatic character.[10]

To the best of our knowledge, no ^{13}C NMR studies of kojic acid or pyrone derivatives have appeared,[11] although Goldstein and co-workers were able to obtain some significant data from the study of ^{13}C satellites in ^1H spectra.[9] The ^{13}C chemical shifts determined in this study are recorded in Table I, and the various ^{13}C–H coupling constants are listed in Table II. In general, the ^{13}C data, like the observations mentioned above, are similar to α,β-unsaturated ketones in some respects and to aromatic heterocycles in other respects. In toto, we feel that these data and the data cited above support the postulate that a degree of aromaticity is present in the 4-pyrone system.

Scheme I illustrates the chemical shifts of kojic acid in relation to various model compounds. In the nonaromatic

Scheme I

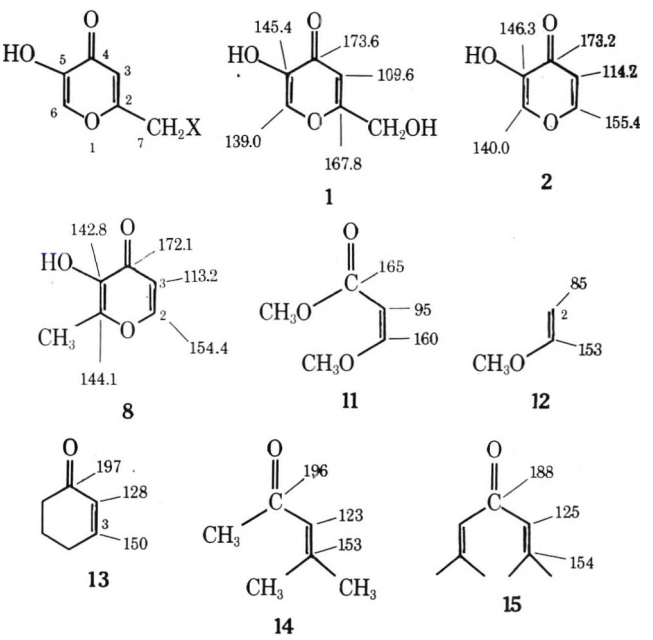
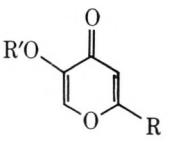


Table I. ^{13}C Chemical Shifts (ppm)[f] and Difference in Chemical Shift vs. a Standard Compound 2 ($\Delta\delta$)[g]



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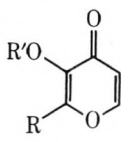

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Registry No.	Compound	R	R′	C-2	C-3	C-4	C-5	C-6[i]	R
501-30-4	1	CH_2OH	H	167.8 (12.2)	109.6 (−4.5)	173.5 (0.5)	145.4 (−1.0)	139.0 (−1)	59.3
496-63-9	2	H	H	155.4	114.2	172.9	146.4	139.9	
7559-81-1	3	CH_2Cl	H	161.5 (6.1)	113.0 (−1.2)	173.4 (0.5)	145.8 (−0.6)	139.8 (0)	41.2
6269-25-6	4[h]	CH_2OH	CH_3[a]	167.7 (12.2)	110.5 (−3.6)	172.5 (−0.4)	147.7 (1.3)	138.2	59.1
40838-34-4	5[h]	CH_2Cl	CH_3[a]	161.4 (6.0)	113.8 (−0.4)		147.8 (1.4)	139.3 (1)	41.0
26209-93-8	6	CH_2OAc[b,d]	Ac[d]	162.7 (7.3)	114.4 (0.1)	171.3 (−1.7)	140.2 (−6.2)	149.0 (9)	60.8
		CH_2OAc[c]	Ac	162.1	114.9	171.9	140.9	147.6	60.8
		CH_2OAc[e]	Ac[e]	164.5	114.1	174.6	140.2	149.9	60.2
499-78-5	7	COOH	H	152.6 (−2.8)	115.6 (1.4)	173.3 (0.5)	147.3 (1.0)	140.4 (0)	160.5
118-71-8	8	CH_3	H	154.3 (−1.1)	113.2 (−1.1)	172.1 (−0.8)	142.6 (−3.8)	148.9 (9)	13.8
1968-51-0	9	CH_2OH	H	154.9 (−0.4)	113.3 (−0.8)	173.1 (0)	142.4 (−4.0)	150.1 (10)	54.9

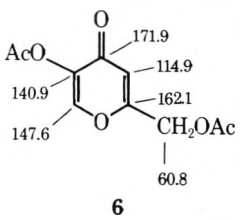
[a] OCH_3 56.1 ppm. [b] Me_2SO-d_6 solution. [c] $CDCl_3$ solution. [d] CH_3CO at 19.9 and 20.3 (CH_3) and 167.3 and 169.4 (CO). [e] $CDCl_3$ plus 1 equiv of TFA. [f] Vs. Me_2SO-d_6 taken as 39.4 ppm from Me_4Si. [g] Data taken from spectra run on a mixture of the compound in question vs. 2. Minor differences may exist with difference in indicated chemical shift vs. that of 2 given in table. [h] $\Delta\delta$ taken from individual spectra, not competitive runs. [i] $\Delta\delta$ values inaccurate owing to broadness of the peak.

model, **13**, C-3 is deshielded because of the resonance effect of carbonyl, which induces a high positive charge density on this carbon.[12] In **12**, the opposite effect is seen for C-2, owing to resonance with the ether oxygen.[13] In **12**, C-1 is strongly deshielded by oxygen. Compound **11**, which contains both carbonyl and ether groups, shows a composite of the effects exhibited by **12** and **13**. The pyrone derivatives **2** and **8** are similar to **11**, but the difference in chemical shift between C-2 and C-3 ($\Delta\delta_{2,3}$ 41 ppm) is much less extreme. The model compounds **14** and **15** show that the effect of one vs. two double bonds conjugated with carbonyl is rather small,[14] and a similar effect is expected in **2** or **8** vs. **11**.[15] The relatively small $\Delta\delta_{2,3}$ for **2** may reflect an evening of charge distribution due to a degree of aromaticity (compare $\Delta\delta_{2,3}$ for furan, 40 ppm, compared to that calculated for methyl propenyl ether, >50 ppm).[16]

The carbonyl resonance is highly shielded in **1** and **2**, and not at all similar to other ketones (e.g., **13–15**).[17] The carbonyl chemical shift is more like that of an ester than a ketone. The shielded nature of the carbonyl is the result of rather low positive charge density on C-4 due to extensive delocalization.[12]

In acid solution, the protonated pyrone system is considered to have a greater degree of aromaticity.[3] However, in Me_2SO-d_6 solutions, not much change in chemical shift of the various carbons was noted upon addition of trifluoroacetic acid (TFA).[13,18] The solvent itself is fairly basic,[19] and the possibility exists that the solvent and substrate were in competition for acid. Most substrates were insoluble in $CDCl_3$, and investigations in this solvent were limited to **6** which was adequately soluble in $CDCl_3$ in both the protonated and unprotonated forms. The chemical shifts of **6** were found to be rather similar in $CDCl_3$ and Me_2SO-d_6. Addition of slightly over 1 equiv of TFA produced a moderate change in the chemical shift of C-2, C-4, and C-6.[17,18] These are precisely the carbons which possess a positive charge in certain resonance forms of the ion **6′**. On the other hand, C-3 and C-5 are slightly shielded.[20] However, the changes in the chemical shifts or coupling constants (Table II) were hardly striking.[17] Although 4-pyrones are reported to be comparatively strong bases,[6] the question remains whether the substrate was fully protonated (as opposed to a hydrogen bond between acid and carbonyl). The instability of the substrate precluded use of a stronger acid.[21]

Scheme II



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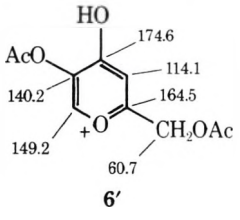


6′

Substituent Effects. The shielding effects of CH_2X and of OR are similar to either alkene or benzene systems (e.g., for CH_3, the α effect is ~9 ppm, and the β effect is −3 ppm; for OH the α effect is ~30 ppm, and the β effect is ~−15 ppm).[22]

With regard to long-range shieldings, comparison of **1** with **2** shows that the CH_2OH group at C-2 shields C-5 by ~1 ppm. In **3**, the CH_2Cl group has a smaller effect. In **8**, the C-6 CH_3 shields C-3 by ~1 ppm (using **2** as a model). On the other hand, a −R substituent, COOH (as in **7**), at C-2 deshields C-5 by 2 ppm. The direction of chemical shift change is similar to aromatic heterocycles, e.g., furan.

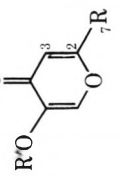
Coupling Constants. Perhaps the most interesting data occur for the coupling constants recorded in Table II. In many cases, it was possible to achieve a complete inventory of coupling constants. The spectra were not simulated, as all coupled protons were separated by large amounts compared to the coupling constants.[23] Signs of coupling constants were not determined, and are not implied in Table II. Structures **2′**, **4′**, and **8′** illustrate typical data.

As in furan,[24] the one-bond coupling constant of the carbon nearest oxygen is near 200 Hz, whereas ^1J for C-3 is much smaller, ca. 167 Hz. In **2**, $^2J_{C3-H2}$ is 8.7 Hz, and $^2J_{C2-H3}$ is 6.5 Hz, similar to pyrone itself.[9] Substitution at C-2 appears to reduce the two-bond coupling constant; in **2**, **8**, and **9** the value is ca. 6.5 Hz, but in **1**, **4**, and **6**, it is ca. 4.7 Hz.

The coupling through O-1 ($^3J_{C2-H6}$ ~ 8 Hz) is comparatively large, similar to findings in pyridine systems.[25,26] The coupling through carbonyl is also quite large ($^3J_{C5-H3}$ ~ 6 Hz). It is noteworthy that sizable ^1H coupling constants were also found by Goldstein et al. in pyrone itself ($^4J_{H2-H6}$ = 1.1 and $^4J_{H3-H5}$ = 2.8 Hz).[9]

The coupling constants involving carbonyl are $^2J_{C4-H3}$ ~

Table II. $^{13}C-^{1}H$ Coupling Constants



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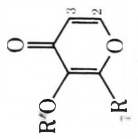

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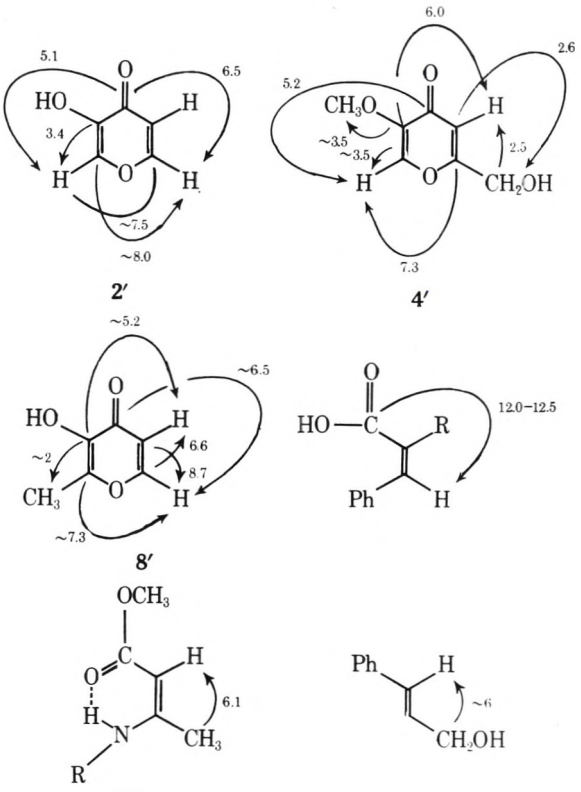
Compd	R	R′	$^{3}J_{C2-H6}$	$^{2}J_{C2-H7}$	$^{2}J_{C2-H3}$	$^{1}J_{C3-H3}$	$^{3}J_{C3-H7}$	$^{2}J_{C4-H3}$	$^{3}J_{C4-H6}$	$^{3}J_{C5-H3}$	$^{2}J_{C5-H6}$	$^{1}J_{C6-H6}$	$^{3}J_{C7-H3}$
1	CH_2OH	H	7.3	~4.7	~4.7	166.5	2.6	1.5	5.1	5.4	3.5	197.5	
2[c]	H	H	7.5		6.5	167		~1.5	5.1	5.5	3.4	198	
4[a]	CH_2OH	CH_3	~7.5	~4.5	~4.5	167.2	2.6	1.4	5.2	6.0	~3.5	198	2.5
6[b]	CH_2OAc	Ac	8.0	~4.9	~4.9	169	2.8	1.5	5.0	6.0	~2.0	201.7	
7	COOH	H	7.9		3.8			1.6	5.0	5.1	3.6	200	3.0
8[d]	CH_3	H			6.6	167.6				5.2			
9[e,g]	CH_2OH	H			6.4	168.0		1.5		5.5			

[a] $^{3}J_{C5-CH_3O} = \sim 3.5$; $^{1}J_{CH_3O-CH_3O} = 144.5$. [b] $^{4}J_{COCH_3-H6} = 0.8$; $^{2}J_{COCH_3-COCH_3} = 7.1$. [c] $^{1}J_{C2-H2} = 199.5$; $^{2}J_{C3-H2} = 8.7$; $^{3}J_{C4-H2} = 5.1$ or 6.5; $^{3}J_{C6-H2} \sim 8$. [d] $^{2}J_{C3-H2} = 8.7$; $^{1}J_{C2-H2} = 199.3$; $^{2}J_{C6-H7} \sim 7.3$; $^{3}J_{C6-H2} \sim 7.3$; $^{3}J_{C5-H7} \sim 2.2$. [e] $^{1}J_{C2-H2} = 197.5$; $^{2}J_{C3-H2} = 8.5$; $^{3}J_{C5-H7} = 2.0$. [f] H-7 is one of the protons of the R group. [g] Tentative assignment for $^{3}J_{C6-H2} \sim 5.6$.

Scheme III



1.5 and $^{3}J_{C4-H6} \sim 5$ Hz. The three-bond coupling constants are the source of a major difference between α,β-unsaturated carbonyl compounds and the pyrone derivatives of this study. In a study of over 20 α,β-unsaturated carbonyl compounds, $^{3}J_{CH}$ for trans nuclei has fallen in the range of 9–16 Hz,[27,28] which is substantially larger than the 5–6-Hz values observed in the pyrones. Representative compounds are shown in Scheme III. In alkenes, couplings between sp^3-hybridized groups (e.g., methyl) and a cis hydrogen are commonly ~6 Hz, whereas in the pyrones the value is ~3 Hz, similar to toluene. In comenic acid (**7**) the coupling constant between COOH and the cis hydrogen is ~3 Hz, substantially less than the 6–7-Hz values found in crotonic acid or cinnamic acid. In pyrones, the electronegative oxygen (O-1) should reduce $^{3}J_{CH}$, but hardly to the extent observed.

Experimental Section

Several possible solvents were tried, but only Me_2SO-d_6 was useful for all compounds. The concentrations used follow: **1**, 0.1 g/ml; **2**, 0.2 g/ml; **3**, 0.1 g/ml; **4**, 0.1 g/ml; **5**, 0.02 g/ml; **6**, 0.2 g/ml (Me_2SO-d_6 or $CDCl_3$, the latter also plus 0.2 and 0.35 ml TFA); **7**, 0.1 g/ml; **8**, 0.2 g/ml; and **9**, 0.1 g/ml. At the request of the referee, mixtures of **2** and each of the other compounds were run where material was available; the concentrations used in these cases was 0.017 g/ml of each component. The latter runs were the source of the $\Delta\delta$ values quoted in Table I. The data were taken on a Varian XL-100 instrument. For the normal runs, as in Table I, a 5K spectral width was used with a 0.4-s acquisition time, a 0.2-s pulse delay, and a 40-μs pulse width (tip angle ~60°). The error in the data acquisition calculated by the computer was 0.09 ppm. Usually 5K of transients were collected. For the data in Table II, a 1 or 2K spectral width was used with 1K filtering. A 4- or 2-s acquisition time was used along with a 1.5-s pulse delay, and a 30–40-μs pulse width. The error in data acquisition calculated by the computer in these cases was 0.5–0.25 Hz depending on spectral width. About 5–10K of transients were collected.

Kojic acid was obtained from Aldrich Chemical Co. For some experiments, an older commercial product was used that had been recrystallized a number of times. Both showed no apparent impurities. Maltol (**8**) was obtained from Fritzsche Bros. This material appeared pure by ^{13}C NMR and further purification was not attempted.

The following compounds were prepared by literature methods.

Pyromeconic acid (3-hydroxy-4-pyrone) (2), mp 116–117 °C (lit.[29] mp 117 °C).

2-Chloromethyl-5-hydroxy-4-pyrone (3), mp 165–166 °C (lit.[30] mp 166–167 °C).

2-Hydroxymethyl-5-methoxy-4-pyrone (5), mp 119–120 °C (lit.[31] mp 119–121 °C).

2-Acetoxymethyl-5-acetoxy-4-pyrone (6). This material was prepared by acetylation of kojic acid, mp 100–102 °C (lit.[32] mp 102 °C).

Comenic Acid (7). This compound was prepared by catalytic oxidation of kojic acid, mp 220 °C dec (lit.[33] mp not specified).

Hydroxymaltol (2-hydroxymethyl-3-hydroxy-4-pyrone) (9), mp 149–151 °C (lit.[34] mp 152–153 °C).

Acknowledgment. Partial funds for the purchase of the Varian XL-100 NMR instrument were provided by NSF Grant GP-10293, which is gratefully acknowledged.

References and Notes

(1) T. Kotani, I. Ichimoto, and C. Tatsumi, *Hakko Kogaku Zasshi,* **51,** 66 (1973).
(2) M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.,* **17,** 256 (1974).
(3) (a) R. F. M. White and H. Williams, "Physical Methods in Heterocyclic Chemistry", Vol. IV, A. R. Katritzky, Ed., Academic Press, New York, N.Y., 1971, pp 228–232; (b) V. Herault and J. Gayoso, *C. R. Acad. Sci., Ser. C,* **269,** 298 (1969); (c) M. J. Cook, A. R. Katritzky, P. Linda, and R. Tack, *Chem. Commun.,* 510 (1970).
(4) F. Feist and E. Baum, *Ber.,* **38,** 3562 (1905).
(5) (a) J. Hirsch, *J. Heterocycl. Chem.,* **12,** 785 (1975); (b) M. A.-F. Elkashef and M. H. Nosseir, *J. Am. Chem. Soc.,* **82,** 4344 (1960). In other work on 4-pyrones, the ketonic oxygen is reported to form no hydrazone or oxime derivative; the molecule is resistant to heat, a fact that became associated with its name; the ketone group is resistant to reduction (A. A. Morton, "The Chemistry of Heterocyclic Compounds", McGraw-Hill, New York, N.Y., 1946, p 150).
(6) H. C. Smitherman and L. Ferguson, *Tetrahedron,* **24,** 923 (1968); this paper reviews all aspects of aromaticity in 4-pyrones.
(7) R. Zahradnik, C. Párkányi, and J. Koutecký, *Collect. Czech. Chem. Commun.,* **27,** 1242 (1962).
(8) R. J. Abraham and W. A. Thomas, *J. Chem. Soc. B,* 127 (1966); A. J. Jones, *Rev. Pure Appl. Chem.,* **18,** 253 (1968); J. A. Elvidge, *Chem. Commun.,* 160 (1965); G. M. Badger, "Aromatic Character and Aromaticity", Cambridge University Press, New York, N.Y., 1969, p 29. (a) N. Brown and P. Bladdon, *Spectrochim. Acta,* **21,** 1277 (1965); (b) J. Jonas, W. Derbyshire, and H. Gutowsky, *J. Chem. Phys.,* **69,** 1 (1965).
(9) (a) R. Mayo and J. H. Goldstein, *Spectrochim. Acta, Part A,* **23,** 55, (1967); (b) C. Mathis and J. H. Goldstein, *ibid.,* **20,** 871 (1964).
(10) R. C. Benson, C. Norris, W. H. Flygare, and P. Beak, *J. Am. Chem. Soc.,* **93,** 5591 (1971). See also H. J. Dauben, J. Wilson, and J. Laity, "Non-Benzenoid Aromatics", Vol. II, J. Snyder, Ed., Academic Press, New York, N.Y., 1971.
(11) K. Kakinuma, C. Hanson, and K. Rinehart, *Tetrahedron,* **32,** 217 (1976).
(12) G. C. Levy and J. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 66.
(13) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, p 183.
(14) J. B. Stothers and P. C. Lauterbur, *Can. J. Chem.,* **42,** 1563 (1964).
(15) Reference 13, p 294, gives data on quinones, for which the CO resonance is also abnormally shielded but not nearly as large as for **1.** See also C. Kingsbury and J. H. Looker, *J. Org. Chem.,* **40,** 1120 (1975).
(16) Reference 13, p 253; see, however, B. Hess Jr., L. Schaad, and C. Holyoke Jr., *Tetrahedron,* **28,** 3657, 5299 (1972) with regard to aromaticity of furan.
(17) Reference 12, p 114.
(18) Reference 12, p 115, shows that TFA causes much greater effect on the CO resonance of acetone (concentration of TFA not specified). See also G. E. Maciel and G. Natterstad, *J. Chem. Phys.,* **69,** 1030 (1965). In ^{1}H spectra, deshieldings of ca. 0.8 ppm for H-3 and ca. 0.5 ppm for H-2 of 4-pyrone have been reported (ref 3), on treatment with TFA.
(19) D. Martin, J. Weise, and H. J. Niclas, *Angew. Chem., Int. Ed. Engl.,* **6,** 318 (1967).
(20) I. Morishima, K. Yoshikawa, K. Okada, T. Yonezawa, and K. Goto, *J. Am. Chem. Soc.,* **95,** 165 (1973).
(21) The solution darkened, and new peaks appeared in the spectrum; the absorptions of the parent compound diminished.
(22) Reference 13, pp 183, 196.
(23) D. W. Mathieson, "Nuclear Magnetic Resonance for Organic Chemists", Academic Press, New York, N.Y., 1967, Chapter 5, suggests that for line separations of large magnitude, a first-order analysis should be adequate (thus for **5,** δ CH_2, 5.0 ppm; δ H-3, 6.56; and δ H-6, 7.99).
(24) Reference 13, p 343.
(25) (a) Y. Takeuchi and N. Dennis, *J. Am. Chem. Soc.,* **96,** 3657 (1974). (b) Roberts and Cristol, however, report small couplings through oxygen: *J. Am. Chem. Soc.,* **95,** 4392 (1973).
(26) For comparison data in benzenoid systems, see (a) F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.,* **89,** 2767 (1976); (b) J. H. Goldstein, V. Watts, and L. Rattet, *Prog. Nucl. Magn. Reson. Spectrosc.,* **8,** 104 (1972); (c) K. Takahashi, T. Sone, and K. Fujieda, *J. Phys. Chem.,* **74,** 2765 (1970).
(27) C. Kingsbury, unpublished results; see also C.-J. Chang, *J. Org. Chem.,* **41,** 1881 (1976).
(28) J. L. Marshall and R. Seiwell, *J. Magn. Reson.,* **15,** 150 (1974), find larger values for $^3J_{CO-H}$.
(29) H. Ost, *J. Prakt. Chem.,* **2,** 19, 177 (1879).
(30) T. Yabuta, *J. Chem. Soc.,* **125,** 575 (1924).
(31) K. N. Campbell, J. F. Ackerman, and B. K. Campbell, *J. Org. Chem.,* **15,** 221 (1950).
(32) K. Maurer, *Chem. Ber.,* **63,** 32 (1930).
(33) C. Stephan, B. Tate, and R. P. Allingham, Belgian Patent 651 427; *Chem. Abstr.,* **64,** 9688e (1966).
(34) F. H. Stodola, *J. Am. Chem. Soc.,* **73,** 5912 (1951).

Reactions of Nitrogen Compounds with Ruthenium Tetroxide. 2. Oxidation of Tertiary Amines as a Convenient Alternative to von Braun Degradation[1]

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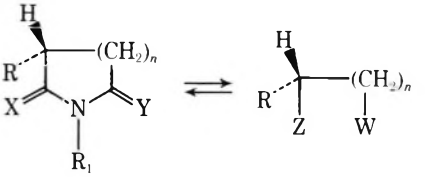
In the course of our previous work on the determination of the absolute configuration of cyclic amines, we correlated (*R*)-(−)-3-methylpiperidine (**1b,** n = 2) with (*R*)-(−)-2-methylglutaric acid (**8b,** n = 2) via (*R*)-(+)-1,5-dibromo-2-methylpentane (**7b,** n = 2), obtained from the benzoyl derivative (**2b,** n = 2) by the von Braun reaction.[2] This scheme could not be used with (*S*)-(+)-3-phenylpiperidine (**1d,** n = 2) and (*S*)-(+)-3-phenylpyrrolidine (**1d,** n = 1), the establishment of whose absolute configuration required much more laborious methods.[3,4]

von Braun's degradation fails with 3-arylamines (**1d**) because of drastic reaction conditions, low yields, and high boiling point of dibromo compound (**7d**). A possible alternative way to the von Braun reaction could be the direct oxidation of cyclic amines with ruthenium tetroxide. Among nitrogen compounds, it has been recently shown that amides[5,6] are oxidized by this reagent, but the few data reported in the literature indicate that only mixtures of intractable products are obtained when amines, without any acyl protection, are reacted with ruthenium tetroxide.[5,7]

In previous work in this field, we observed that ruthenium tetroxide has a low reactivity with the benzyl carbon attached to the nitrogen both in benzyllactams[8] and in *N*-acylamides having a phenyl group on the tertiary carbon adjacent to the nitrogen.[6] On the basis of this, we used ruthenium tetroxide to oxidize the *N*-benzyl derivatives of piperidines (**3a–d,** n = 2) and of pyrrolidines (**3a,d,** n = 1). This gave the corresponding imides (**6**), which were identified by their analytical and spectral characteristics, hydrolysis to the dicarboxylic acids (**8**), and by comparison with reference compounds prepared from the monoamides (**9**).

A very high optical yield was obtained in the oxidation of optically active amines. Hydrolysis of the imide *R*-(+)-**6b** (n = 2), obtained from *R*-(−)-**3b,** gave optically pure (*R*)-(−)-2-methylglutaric acid.[2] Analogously, the amines *S*-(−)-**3d** (n = 1, 2) gave the corresponding imides, which showed an optical rotation with the same sign as, but of a higher absolute



$X = Y = H_2$ $R_1 = C_6H_5CH_2$

1, R_1 = H; **2,** R_1 = C_6H_5CO; **3,** R_1 = $C_6H_5CH_2$; **4,** X = O; Y = CH_2; **5,** Y = O; X = CH_2; **6,** X = Y = O; **7,** Z = W = CH_2Br; **8,** Z = W = COOH; **9,** Z = COOH; W = $CONHCH_2C_6H_5$

a, R = H; **b,** R = CH_3; **c,** R = C_2H_5; **d,** R = C_6H_5 (n = 1, 2)

value than, that of the imides obtained by acidic cyclization of monobenzylamides (**9d**) obtained by the action of benzylamine on phenylglutaric and phenylsuccinic acid anhydrides belonging to the *S* series.

The oxidation was carried out at room temperature in a mixture of carbon tetrachloride and water containing an excess of sodium metaperiodate and a catalytic amount of ruthenium dioxide hydrate. After vigorous stirring for about 20 h, the *N*-benzylimides (**6**) were isolated in yields of around 50%. When the reaction time or the amount of sodium metaperiodate was reduced, the intermediate lactams (**4** and **5**) could be isolated from the reaction mixture.

The unsubstituted amines (**3a**) and the amines containing an alkyl group (**3b,c**) are oxidized much faster than the phenyl-substituted ones (**3d**). In fact, the reaction mixture of the latter contained monooxidized products even after a reaction for 80 h in the presence of an excess of sodium metaperiodate, these products being easily separated from the *N*-benzylimides by chromatography on a silica column.

These results show that *N*-benzylpiperidines and pyrrolidines having a substituent in the 3 position are oxidized by ruthenium tetroxide under very mild conditions, which permits their absolute configuration to be correlated with that of substituted glutaric and succinic acids. This reaction confirms the absolute configurations assigned before in a different manner[2-4] and therefore represents a convenient alternative to von Braun degradation of cyclic amines.

Experimental Section

Microanalyses were carried out by Dr. De Leonardis R., Istituto di Chimica Farmaceutica, Bari, with a Hewlett-Packard Model 185 C, H, N analyzer. The melting points, determined with a Buchi-Tottoli capillary melting point apparatus, are uncorrected. Optical rotations were determined on a Roussel-Jouan electronic micropolarimeter. Infrared, ^{1}H NMR, and mass spectra were determined with a Perkin-Elmer Model 257, a Varian HA-100, and a Perkin-Elmer Model 270 spectrometers, respectively. NMR chemical shifts are expressed in δ with Me_4Si as internal standard.

***(R,S)*-*N*-Benzyl-3-ethylpiperidine (3c, *n* = 2).** 3-Ethylpiperidine[9] (obtained from catalytic reduction[10] of the corresponding pyridine) was refluxed with equimolecular amounts of benzyl chloride and triethylamine. Compound **3c** (n = 2) was obtained, bp 89 °C (0.8 mm), hydrochloride mp 146 °C (EtOH).

Anal. Calcd for $C_{14}H_{21}N$·HCl: C, 70.12; H, 9.25; N, 5.84. Found: C, 70.36; H, 9.17; N, 5.67.

***(S)*-(−)-*N*-Benzyl-3-phenylpiperidine (3d, *n* = 2).** (*S*)-(+)-3-Phenylpiperidine (optical purity 97%),[3] treated as described above, gave the benzyl derivative: mp 53 °C (EtOH–H_2O); $[\alpha]_D$ −41° (MeOH); NMR ($CDCl_3$) δ 1.1–3.0 (9 H, m, alicyclic H), 3.49 (2 H, s, benzylic CH_2), 7.0–7.4 (10 H, m, aromatic H); mass spectrum *m/e* 251 (M^+).

Anal. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.84; H, 8.61; N, 5.52.

***N*-Benzylpiperidine-2,6-dione (6a, *n* = 2).** *N*-Benzylpiperidine (**3a**, n = 2, 1.90 g)[11] in CCl_4 (70 ml) was added with stirring to a solution of sodium metaperiodate (8.50 g) in water (100 ml) in the presence of ruthenium dioxide hydrate (0.10 g). After 24 h at room temperature, the aqueous layer was extracted several times with CCl_4 and the combined organic phases, after the elimination of RuO_4 with 2-propanol and filtration, were worked up in the usual way to give *N*-benzylpiperidine-2,6-dione (0.92 g, 41%), which was distilled under reduced pressure: ir (neat) 1725, 1675 cm^{-1}; NMR (CCl_4) δ 1.6–1.9 (2 H, m, 4-H), 2.44 (4 H, t, J = 6 Hz, 3,5-H), 4.74 (2 H, s, benzylic CH_2), 7.02–7.27 (5 H, m, aromatic H).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.23; H, 6.73; N, 6.71.

***(R)*-(+)-*N*-Benzyl-3-methylpiperidine-2,6-dione (6b, *n* = 2).** Optically pure (*R*)-(−)-*N*-benzyl-3-methylpiperidine (**3b**, n = 2)[10] was oxidized as described above. The crude reaction mixture was purified by distillation under reduced pressure to give **6b** (n = 2) (70%), $[\alpha]_D$ +34.9° (CCl_4), which was shown to be identical with a sure sample obtained from 2-methylglutaric acid: ir (neat) 1725, 1675 cm^{-1}; NMR (CCl_4) δ 1.19 (3 H, d, J = 7 Hz, methyl H), 1.28–1.96 (2 H, m, 4-H), 2.18–2.72 (3 H, m, 3,5-H), 4.74 (2 H, s, benzylic CH_2), 7.0–7.3 (5 H, m, aromatic H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.91; H, 7.20; N, 6.33.

The hydrolysis of the imide **6b** (n = 2) with concentrated HCl under reflux (5 h) gave optically pure (*R*)-(−)-2-methylglutaric acid (100%).[2]

***(R,S)*-*N*-Benzyl-3-ethylpiperidine-2,6-dione (6c, *n* = 2).** (*R,S*)-*N*-Benzyl-3-ethylpiperidine (**3c**, n = 2) was oxidized as described above. The crude reaction mixture (90%) was purified by distillation and compound **6c** (n = 2) was obtained (58%): bp 140–148 °C (1.2 mm); ir (neat) 1730, 1680 cm^{-1}; NMR (CCl_4) δ 0.91 (3 H, t, J = 8 Hz, methyl H), 1.05–2.0 (4 H, m, 4 and CH_2CH_3 H), 2.05–2.8 (3 H, m, 3,5-H), 4.78 (2 H, s, benzylic CH_2), 7.0–7.4 (5 H, m, aromatic H).

The hydrolysis of the imide, performed as described above, gave 2-ethylglutaric acid (92%).[12]

***(S)*-(−)-*N*-Benzyl-3-phenylpiperidine-2,6-dione (6d, *n* = 2).** (*S*)-(+)-2-Phenylglutaric acid[13] (**8d**, n = 2) (optical purity 96%) was converted into the anhydride[14] which showed $[\alpha]_D$ +40.5° (absolute EtOH). By treatment of the anhydride with benzylamine in dry ether,[15] the benzylammonium salt of the acid (**9d**, n = 2) was obtained: mp 131 °C (EtOH–Et_2O); $[\alpha]_D$ +14.6° (absolute EtOH).

Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.25; H, 6.94; N, 6.64.

By treatment with 6 N HCl, the benzylammonium salt gave 2-phenyl-5-benzylamidoglutaric acid (**9d**, n = 2): mp 145–147 °C (EtOH–Et_2O); $[\alpha]_D$ +62° (absolute EtOH); ir (KBr) 3340, 1725 cm^{-1}; NMR (CD_3OD) δ 1.9–2.3 (4 H, m, 3,4-H), 3.50 (1 H, t, J = 7 Hz, 2-H), 4.24 (2 H, s, benzylic CH_2), 4.96 (exchangeable H), 7.08–7.34 (10 H, m, aromatic H).

The amide was dehydrated[16] by refluxing (30 min) with glacial acetic acid–concentrated sulfuric acid (9:1) to give the imide **6d** (n = 2): mp 69–70 °C (C_6H_6–*n*-C_6H_{14}): $[\alpha]_D$ −1.7° (absolute EtOH, c 7%); ir (KBr) 1720, 1670 cm^{-1}; NMR (CCl_4) δ 1.8–2.1 (2 H, m, 4-H), 2.3–2.5 (2 H, m, 5-H), 3.55 (1 H, t, J = 6 Hz, 3-H), 4.82 (2 H, s, benzylic CH_2), 6.8–7.4 (10 H, m, aromatic H).

In the same way from (*R,S*)-2-phenylglutaric acid, the racemic imide (**6d**, n = 2) having ir and NMR spectra identical with those of the optical isomer was obtained.

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.61; H, 6.15; N, 4.93.

Compound **6d** (n = 2) was also obtained (25%) by oxidation (80 h) with ruthenium tetroxide of (*S*)-(−)-*N*-benzyl-3-phenylpiperidine (**3d**, n = 2), after chromatographic purification of the crude reaction mixture (67%) as described above: mp 59 °C (C_6H_6–*n*-C_6H_{14}); $[\alpha]_D$ −9.8° (absolute EtOH); ir and NMR spectra were identical with those shown by the same product obtained from **8d** (n = 2).

***N*-Benzylpyrrolidine-2,5-dione (6a, *n* = 1).** *N*-Benzylpyrrolidine (**3a**, n = 1)[17] was oxidized as described above. The crude reaction mixture (62%) was purified by chromatography on silica to give compound **6a** (n = 1) (32%): mp 98–99 °C (EtOH); ir (CH_3CN) 1775, 1705 cm^{-1};[18] NMR ($CDCl_3$) δ 2.6 (4 H, s, alicyclic H), 4.56 (2 H, s, benzylic CH_2), 7.16–7.34 (5 H, m, aromatic H).

***(S)*-(+)-*N*-Benzyl-3-phenylpyrrolidine-2,5-dione (6d, *n* = 1).** (*S*)-(+)-2-Phenylsuccinic acid[19] (**8d**, n = 1) (optical purity 94%) was converted into the anhydride,[15] mp 81–82 °C, $[\alpha]_D$ +97.5° (Me_2CO), and then in the corresponding 2-phenyl-4-benzylamidosuccinic acid benzylammonium salt as described above: mp 155 °C (EtOH–Et_2O); $[\alpha]_D$ +62° (Me_2CO).

Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.18. Found: C, 73.53; H, 6.86; N, 6.80.

By treatment with 6 N HCl the salt gave the corresponding monobenzylamide (**9d**, n = 1): mp 135 °C (EtOH–Et_2O); $[\alpha]_D$ +88.6° (Me_2CO); ir (KBr) 1710, 1610 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.71; H, 6.02; N, 4.63.

The amide was dehydrated as described above to give the imide (**6d**, n = 1): mp 60 °C (EtOH); $[\alpha]_D$ +38° ($CHCl_3$);[20] ir (KBr) 1775, 1700 cm^{-1}; NMR ($CDCl_3$) δ 2.72 and 3.10 (2 H, AB part of ABX system, J_{AB} = 18 Hz, 4-H), 3.87 (1 H, q, X part, 3-H), 4.66 (2 H, s, benzylic CH_2), 7.0–7.5 (10 H, m, aromatic H).

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.91; H, 5.71; N, 5.17.

Compound **6d** (n = 1) was also obtained from (*S*)-(−)-*N*-benzyl-3-phenylpyrrolidine (**3d**, n = 1)[4] having $[\alpha]_D$ −29° (MeOH, optical purity 74%) by oxidation (80 h) with ruthenium tetroxide as described above. The crude reaction mixture (70%), chromatographed on silica, gave the imide (26%): mp 65–67 °C (EtOH); $[\alpha]_D$ +34.5 °C ($CHCl_3$);[20] ir and NMR spectra identical with those shown by the same product obtained from **8d** (n = 1).

Registry No.—**1c** (n = 2), 59433-08-8; **1d** (n = 2), 59349-71-7; **3a** (n = 1), 29897-82-3; **3a** (n = 2), 2905-56-8; **3b** (n = 2), 37675-26-6; **3c** (n = 2), 59349-72-3; **3c** (n = 2) HCl, 59349-73-4; **3d** (n = 1), 59349-74-5; **3d** (n = 2), 59349-75-5; **6a** (n = 1), 2142-06-5; **6a** (n = 2), 42856-43-9; **6b** (n = 2), 59349-76-7; **6c** (n = 2), 59349-77-8; **6d** (n = 1), 59349-78-9; **6d** (n = 2), 59349-79-0; (±)-**6d** (n = 2), 59433-09-9; **8d**, (n = 1), 4036-30-0; **8d** (n = 2), 59349-80-3; **9d** (n = 1), 59349-81-4; **9d** (n = 1) $PhCH_2NH_2$, 59349-82-5; **9d** (n = 2), 59349-83-6; **9d** (n = 2) $PhCH_2NH_2$, 59349-84-7.

References and Notes

(1) For the previous article in this series, see ref 6.
(2) G. Bettoni, R. Perrone, and V. Tortorella, *Gazz. Chim. Ital.*, **102**, 196 (1972).
(3) F. Morlacchi, M. D'Ambruoso, and V. Tortorella, *Chim. Ind. (Milan)*, **56**, 465 (1974).
(4) G. Bettoni, C. Cellucci, and V. Tortorella, *Chim. Ind. (Milan)*, **56**, 465 (1974).
(5) J. C. Sheehan and R. W. Tulis, *J. Org. Chem.*, **39**, 2264 (1974).
(6) N. Tangari and V. Tortorella, *J. Chem. Soc., Chem. Commun.*, 71 (1975).
(7) L. M. Berkowitz and P. N. Rylander, *J. Am. Chem. Soc.*, **80**, 6682 (1958).
(8) Unpublished results obtained in our laboratory.
(9) H. Cottin, *Bull. Soc. Chim. Fr.*, 2729 (1966).
(10) G. Bettoni, E. Duranti, and V. Tortorella, *Gazz. Chim. Ital.*, **102**, 189 (1972).
(11) C. Schotten, *Ber.*, **15**, 421 (1882).
(12) M. F. Ansell and D. H. Hey, *J. Chem. Soc.*, 1683 (1950).
(13) L. Westman, *Ark. Kemi*, **11**, 431 (1957).
(14) K. Kawazu, T. Fujita, and T. Mitsui, *J. Am. Chem. Soc.*, **81**, 932 (1959).
(15) M. Naps and I. B. Johns, *J. Am. Chem. Soc.*, **62**, 2450 (1940).
(16) G. Casini, M. Ferappi, D. Misiti, and A. Schimberni, *Ann. Chim. (Rome)*, **49**, 1791 (1959).
(17) J. Schlinck, *Ber.*, **32**, 947 (1899).
(18) T. Matsuo, *Bull. Chem. Soc. Jpn.*, **37**, 1844 (1964).
(19) A. Fredga, J. P. Jennings, W. Klyne, P. M. Scopes, B. Sjoberg, and S. Sjoberg, *J. Chem. Soc.*, 3928 (1965).
(20) A less soluble racemate separates during crystallization; however, it is clear that a more extensive racemization occurs in the cyclization reaction.

Formation of Nitrate Esters by the Oxidation of Alkenes and Cyclopropanes with Thallium(III) Nitrate in Pentane[1]

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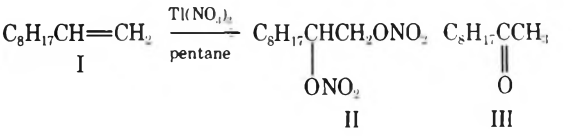
Nitrate esters are potentially useful synthetic intermediates for which few general methods of preparation are known. The corresponding alcohol may be esterified using nitric acid[2] alone or in a variety of cosolvents.[3-9] The corresponding halide can be metathetically converted to a nitrate ester using silver nitrate under heterogeneous[10-12] or homogeneous conditions.[13,14] More recently nitrates have been formed by mercury assisted solvolysis of alkyl halides.[15]

In our studies of the oxythallation and solvolytic dethallation of olefins by thallium(III) nitrate in methanol, we noted that nitrate esters are formed[16] in addition to the expected methyl ethers and carbonyl products.[17,18] As a result reaction conditions were sought under which the major product would be nitrate esters. Diethyl ether, dimethyl sulfoxide, sulfolane, and dimethylformamide all cause decomposition of the thallium(III) nitrate. Glyme, diglyme, and dioxane dissolve the thallium(III) nitrate to form stable solutions only if 1% nitric acid is added. Despite the fact that thallium(III) nitrate is very insoluble in pentane, the oxidation of the olefin does occur quite readily in this solvent.

In a typical reaction, a solution of the olefin in pentane is added to a stirred heterogeneous pentane–thallium(III) nitrate mixture maintained at room temperature. For most reactions a 10% excess of the oxidizing agent is used. Because of the relative instability of nitrate esters the reaction is terminated when it appears to be complete. The progress of the reaction can be qualitatively monitored by observing the change in the physical state of the thallium reagent.

Oxidation of 1-decene occurs in 1 h to give 1,2-decanediol dinitrate (II) in 85% yield. The remaining product is 2-decanone (III) which arises from a hydride shift in the dethallation



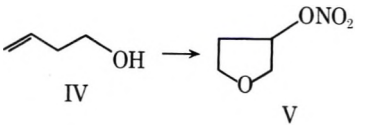
step. Thus a substantial decrease in rearranged product is observed compared to when methanol is the solvent in which yields of 34–40% 2-decanone are obtained.[16]

Reaction of *trans*-stilbene requires 72 h and leads to a mixture of *meso*- and *dl*-1,2-diphenyl-1,2-ethanediol dinitrate. Analysis of the mixture by using NMR resonances described earlier[16] indicates that the meso/*dl* ratio is 2:1. The reaction in methanol was found to be stereospecific.[16] There was no evidence of any rearranged products such as noted in the reaction in methanol.

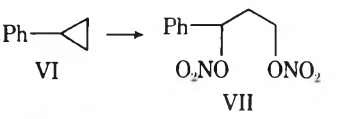
Oxidation of cyclohexene in pentane occurs in 4 h to give *cis*- and *trans*-1,2-cyclohexanediol dinitrate (85%) and cyclopentanecarboxaldehyde (15%). The trans/cis ratio as determined by NMR is approximately 2/1. The resonance of the cis isomer (δ 5.10–5.55) and the trans isomer (δ 4.82–5.28) overlap somewhat and limit the accuracy of this method. The products contrast strongly with the results obtained in methanol where cyclopentanecarboxaldehyde is the major product.[17]

The *cis*- and *trans*-5-decenes react extremely slowly. After 11 days the cis isomer gave a mixture of *meso*- and *dl*-5,6-decanediol dinitrates in 64% yield with the remainder being 16% unreacted olefin, 9% 5-decanone, and 11% unidentified minor components. The trans isomer reacted more slowly. After 12 days a 38% yield of the *meso*- and *dl*-5,6-decanediol dinitrates was formed. The remaining material was 30% starting olefin, 17% 5-decanone, and 15% unidentified minor components. As the reaction time was increased, decomposition of product occurred with the evolution of NO_2. The exact percentages of the two dinitrate products were not determined.

3-Buten-1-ol (IV) reacts in 1 h to form exclusively 3-hydroxytetrahydrofuran nitrate ester (V). The product was isolated in 89% yield. There is no evidence of any open chain product.



Since we have noted similarities in the reaction of thallium(III) acetate with alkenes[19] and cyclopropanes[20] the oxidative cleavage of a cyclopropane by thallium(III) nitrate was examined. Phenylcyclopropane (VI) reacts in 12 h to give exclusively 1-phenyl-1,3-propanediol dinitrate (VII) which



was isolated in 91% yield. There was no evidence of the symmetrically cleaved product, 2-phenyl-1,3-propanediol dinitrate.

The results of this study may be summarized as (1) oxythallation in pentane occurs readily to yield nitrate esters, (2) rearrangement products occur to a lesser extent in pentane than in methanol, and (3) there is a loss of stereospecificity in pentane as solvent.

Experimental Section

General Method for Preparation of Nitrate Esters. Authentic samples of nitrate esters were prepared by slowly adding an acetic acid–water–fuming nitric acid mixture (1.5:1.5:1) to a solution of the proper alcohol in an acetic acid–water mixture (1:1). The reaction mixture was maintained at 0 °C for approximately 1 h. Water was added and the mixture was extracted with ether. The desired nitrate ester was isolated and purified by either distillation or crystallization.

General Procedure for Oxythallations in Pentane. A pentane solution of the olefin was added slowly to a stirred heterogeneous pentane solution, containing a 10% excess of thallium(III) nitrate, maintained at room temperature. Reaction times vary according to the reactivity of the compound. The progress of the reaction is monitored by observing the change in the physical state of the thallium reagent. Upon completion of the reaction, the pentane solution was diluted with ether and the organic layer was washed repeatedly with water. After drying over magnesium sulfate, the solution was filtered and the solvent was removed under reduced pressure. The crude product was then examined by NMR. Purified samples of the products were obtained by elution through silica gel columns.

Preparation of 3-Hydroxytetrahydrofuran Nitrate Ester. Nitration of 3-hydroxytetrahydrofuran was accomplished by the described general method. Distillation afforded 2.9 g (47%) of the ester as a clear liquid: bp 59–61 °C (4 mm); ^{1}H NMR (CCl_4) δ 5.36–5.70 m (1), 3.64–4.17 m (4), 1.74–2.67 m (2).

Anal. Calcd for $C_4H_7NO_4$: C, 36.10; H, 5.30; N, 10.52. Found: C, 35.89; H, 5.25; N, 10.57.

Preparation of *cis*-Cyclohexanediol Dinitrate. Nitration of *cis*-cyclohexanediol by the general method described gave the nitrate ester which was crystallized at 0 °C from petroleum ether: mp 23–24 °C (lit.[21] 24.5–25 °C); ^{1}H NMR (CCl_4) δ 5.10–5.55 m (2), 1.33–2.31 m (8).

Preparation of *trans*-Cyclohexanediol Dinitrate. Nitration of *trans*-cyclohexanediol by the general method described gave the nitrate ester which was crystallized at 0 °C from petroleum ether: mp 17–18 °C (lit.[21] 17.5–18 °C); ^{1}H NMR (CCl_4) δ 4.82–5.28 m (2), 1.32–2.53 m (8).

Preparation of *dl*-5,6-Decanediol Dinitrate. The title compound was prepared from *dl*-5,6-decanediol by the general method described. Distillation afforded a slightly yellow liquid: bp 112–113 °C (1.4 mm); ^{1}H NMR (CCl_4) δ 5.01–5.41 m (2), 1.25–2.04 m (12), 0.70–1.25 m (6).

Anal. Calcd for $C_{10}H_{20}N_2O_6$: C, 45.44; H, 7.63; N, 10.61. Found: C, 45.34; H, 8.18; N, 10.47.

Preparation of *meso*-5,6-Decanediol Dinitrate. *meso*-5,6-Decanediol was nitrated by the general method described. Distillation afforded a slightly yellow liquid: bp 107–108 °C (1.0 mm); ^{1}H NMR (CCl_4) δ 5.09–5.46 m (2), 1.29–2.12 m (12), 0.71–1.29 m (6).

Anal. Calcd for $C_{10}H_{20}N_2O_6$: C, 45.44; H, 7.63; N, 10.61. Found: C, 45.23; H, 8.25; N, 10.46.

Registry No.—Thallium(III) nitrate, 13746-98-0; 3-hydroxytetrahydrofuran nitrate, 59331-87-2; 3-hydroxytetrahydrofuran, 453-20-3; *cis*-cyclohexanediol dinitrate, 32342-28-2; *cis*-cyclohexanediol, 1792-81-0; *trans*-cyclohexanediol dinitrate, 32342-29-3; *trans*-cyclohexanediol, 1460-57-7; *dl*-5,6-decanediol dinitrate, 59331-88-3; *dl*-5,6-decanediol, 59367-33-8; *meso*-5,6-decanediol dinitrate, 59331-89-4; *meso*-5,6-decanediol, 58581-15-0; pentane, 109-66-0.

References and Notes

(1) This paper was abstracted from the Ph.D. Thesis of R. J. Bertsch, The Ohio State University, 1975.
(2) R. Boschan, R. Merrow, and R. W. van Dolah, *Chem. Rev.*, **55**, 485 (1955).
(3) D. R. Goddard, E. D. Hughes, and C. K. Ingold, *Nature (London)*, **158**, 480 (1946).
(4) D. R. Goddard, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2559 (1950).
(5) C. K. Ingold, D. J. Miller, and H. G. Poole, *J. Chem. Soc.*, 2576 (1950).
(6) E. L. Blackall, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 4366 (1958).
(7) A. Topchiev, "Nitration of Hydrocarbons and Other Organic Compounds", Pergamon Press, Oxford, 1959.
(8) F. Kaufman, K. J. Cook, and S. M. David, *J. Am. Chem. Soc.*, **74**, 4997 (1952).
(9) J. E. Lufkin, U.S. Patent 2 396 330 (1946); *Chem. Abstr.*, **40**, 3462 (1946).
(10) N. Kornblum, N. N. Lichtin, J. T. Patton, and D. C. Iffland, *J. Am. Chem. Soc.*, **69**, 307 (1947).
(11) J. W. Baker and D. M. Easty, *J. Chem. Soc.*, 1193 (1952).
(12) E. Gand, *Bull. Soc. Chim. Fr.*, 120 (1950).
(13) L. F. Fieser and W. von E. Doering, *J. Am. Chem. Soc.*, **68**, 2252 (1946).
(14) A. F. Ferris, K. W. McLean, I. G. Marks, and W. D. Emmons, *J. Am. Chem. Soc.*, **75**, 4078 (1953).
(15) A. McKillop and M. E. Ford, *Tetrahedron*, **30**, 2467 (1974).
(16) R. J. Bertsch and R. J. Cuellette, *J. Org. Chem.*, **39**, 2755 (1974).
(17) A. McKillop, J. D. Hunt, E. C. Taylor, and F. Kienzle, *Tetrahedron Lett.*, 5275 (1970).
(18) A. McKillop, J. D. Hunt, F. Kienzle, E. Bigham, and E. C. Taylor, *J. Am. Chem. Soc.*, **95**, 3635 (1973).
(19) R. J. Ouellette, G. Kordosky, C. Levin, and S. Williams, *J. Org. Chem.*, **34**, 4104 (1969).
(20) A. South, Jr., and R. J. Cuellette, *J. Am. Chem. Soc.*, **90**, 7064 (1968).
(21) K. S. Ennor and J. Heneyman, *J. Chem. Soc.*, 2586 (1958).

2,2-Bis(trifluoromethyl)-1,2-dihydropyrimidinium Salts

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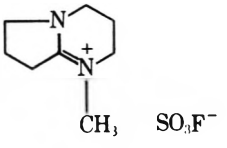
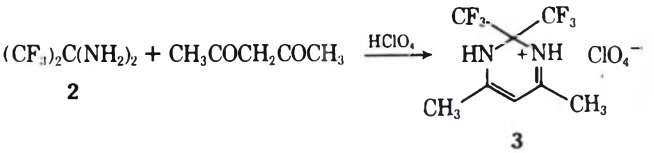
Although quite a few organic compounds are satisfactory for use as laser dyes in the visible and infrared regions of the spectrum,[1] no compounds of comparably high efficiency are known for the ultraviolet region. It occurred to us that since many laser dyes are cyanine or merocyanine dyes with rigid structures, compounds of this type with short conjugation might prove interesting as laser dyes. The first short-chain cyanine that we prepared, compound **1**, showed no fluores-



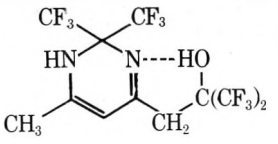
1

cence. This may be due to quenching by the solvent (alcohol), since the fluorescence would be expected at lower than 300 nm. A simple, higher vinylog of **1** is a 1,2-dihydropyrimidine derivative, and the most direct method for the synthesis of a compound of this type is through the condensation of a 1,3-dicarbonyl derivative with a geminal diamine. An example of a stable geminal diamine is the hexafluoro derivative **2**,[2] and in spite of the strong deactivation of the amino groups, we hoped to carry out the following reaction.



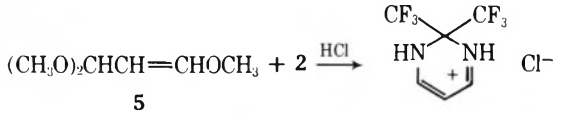
2 **3**

Problems were encountered in obtaining **3**, but a procedure was finally devised that gave **3** in 35% yield along with about a 20% recovery of the perchlorate salt of **2** and 40% of a by-product, which was shown to have the structure **4**. The latter compound presumably is formed by the condensation of **3** with hexafluoroacetone, which is formed by hydrolysis of **2**.



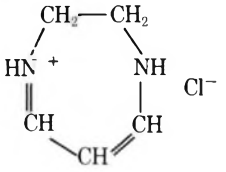
4

The dihydropyrimidine derivative **6** was prepared from **5** and **2**. This condensation worked well in benzene and hydrogen chloride in contrast to the reaction with acetylacetone, which gave a product that was difficult to purify.



5 6

Compounds **3** and **6** showed violet fluorescence in water and had only one absorption peak at 347 nm (ϵ 5000) and 355 (5000), respectively, in water. They fluoresce blue-violet in water, ethanol, and hexafluoro-2-propranol. The fluorescence maximum of **3** is at 398 nm in ethanol. On excitation with the second harmonic of a Q-switched ruby laser (λ 347 nm), **3** lases efficiently at 408 nm in water. The fluorescence of **3** and **6** is in direct contrast to the behavior of **7**, which shows no fluorescence in water or other solvents. The nonfluorescence of **7** probably is due to the nonplanarity of the molecule.



7

Attempts to prepare the *N,N'*-dimethyl derivative of **3**, either by methylation of a neutralized solution of **3** with methyl fluorosulfonate or by the condensation of acetylacetone and the *N,N'*-dimethyl derivative of **2**, were unsuccessful.

Experimental Section

Melting points were determined in a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were recorded on a Cary 14 spectrometer. Proton spectra were recorded with a Bruker HX-90 instrument and ^{13}C NMR spectra were recorded on a Bruker HX-90 equipped with a Digilab data system at 22.63 MHz. The NMR spectra were run in Me_2SO vs. Me_4Si.

4,6-Dimethyl-2,2-bis(trifluoromethyl)-1,2-dihydropyrimidinium Perchlorate (3). To a solution of 5 g (0.0274 mol) of **2** and 2.74 g (0.0274 mol) of acetylacetone in 25 ml of tetrahydrofuran was added 3.56 g (0.0274 mol) of 70% perchloric acid. The solution was allowed to stand in a 50-ml Erlenmeyer flask until the solvent had evaporated (about 2 weeks). The residue was extracted with 100 ml of hot isopropyl alcohol and filtered hot. The insoluble material (1.5 g) had an ir absorption curve that was identical with that of the perchlorate salt of the diamine **2**. The alcohol solution was evaporated to dryness and the residue was stirred with ether. The white, insoluble crystals of **3** were collected and recrystallized from 1,2,3-trichloropropane: yield 2.9 g; mp 198–200 °C. The ^1H NMR spectrum showed CH_3 (s, 6 H) at δ 2.18, CH (s, 1 H) at δ 5.4, and NH broad at δ 7.2 ppm.

Anal. Calcd for $C_8H_9ClF_6N_2O_4$: C, 27.7; H, 2.6; N, 8.1. Found: C, 27.5; H, 2.5; N, 8.2.

The ether filtrate was evaporated to dryness and the residue was recrystallized from heptane giving 3.2 g of **4**, mp 93–94 °C. The ^1H NMR spectrum showed CH_3 (s, 3 H) at δ 2.18, CH_2 (s, 2 H) at δ 2.98, CH (s, 1 H) at δ 5.05, and NH and OH broad at δ 5.0 and 8.1 ppm. The ^{13}C NMR spectrum showed C_4, 169; C_6, 155.4; CF_3 as two quartets centered at 123.5 and 121.5; C_5, 92.1, COH and C_2, multiplet centered at 76.7; CH_2, 34.0; and CH_3, 18.7 ppm.

Anal. Calcd for $C_{11}H_8F_{12}N_2O$: C, 32.1; H, 1.7; N, 6.8. Found: C, 31.9; H, 1.9; N, 6.8.

2,2-Bis(trifluoromethyl)-1,2-dihydropyrimidinium Chloride (6). Hydrogen chloride was passed through a solution of 5 g of **2** and 3.7 g of 1,3,3-trimethoxy-1-propene in 500 ml of dry benzene for 5 min. After the mixture had stood overnight, the solid was collected and washed with ether: yield 4 g; mp 185 °C dec. The ^{13}C NMR showed C_4 and C_6, 156; CF_3 as a quartet centered at 121; C_5, 91.8; and C_2, as a multiplet at 74.6 ppm.

Anal. Calcd for $C_6H_5ClF_6N_2$: C, 28.3; H, 2.0; N, 11.0. Found: C, 28.6; H, 2.3; N, 11.4.

Acknowledgment. We are grateful for the assistance of Dr. P. M. Henrichs, who interpreted the ^{13}C spectrum of **4** and suggested this structure.

Registry No.—**2**, 1737-80-0; **3**, 59389-77-4; **4**, 59389-78-5; **5**, 17576-35-1; **6**, 59389-79-6; acetylacetone, 123-54-6.

References and Notes

(1) K. H. Drexhage in "Topics in Applied Physics", Vol. I, F. P. Schafer, Ed., Springer-Verlag, West Berlin, 1973, p 144.
(2) W. J. Middleton and C. J. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).

Photochemical Transformation of 7-Benzoyl-7,8-epoxydibenzobicyclo[2.2.2]octa-2,5-diene

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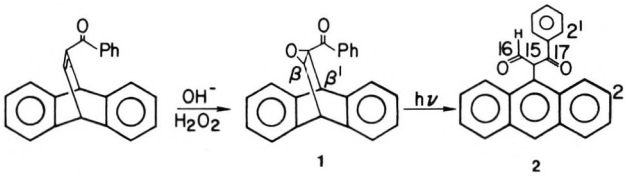
Investigations of a number of α,β-epoxy ketones have demonstrated that these species are exceptionally reactive under the influence of ultraviolet light. It has been shown that irradiation of these compounds may lead to geometrical isomerization, internal hydrogen abstraction, and rearrangement.[1] We have observed a novel, unanticipated photoisomerization of the title compound (**1**) which represents a new diversion in α,β-epoxy ketone rearrangement.

Base-catalyzed epoxidation of 7-benzoyldibenzobicyclo[2.2.2]octatriene[2] with hydrogen peroxide gave the title epoxy ketone (**1**), mp 191–192 °C. Irradiation of a 2% solution of the epoxy ketone **1** in dry benzene in a quartz reactor with



1 2

unfiltered light from a medium-pressure lamp in a nitrogen atmosphere for 14 h yielded an isomeric (M^+ 324), golden yellow compound, mp 163–165 °C, in about 70% yield.

A complex absorption pattern at 1600 cm^{-1} in the infrared indicated an enolizable 1,3-dicarbonyl functionality in the photoproduct.[3] A broad band at 2850 cm^{-1} was suggestive of a possible C–H stretch of an aldehyde group. The electronic spectrum of the photoproduct was very similar to that of a 9-substituted anthracene.[4]

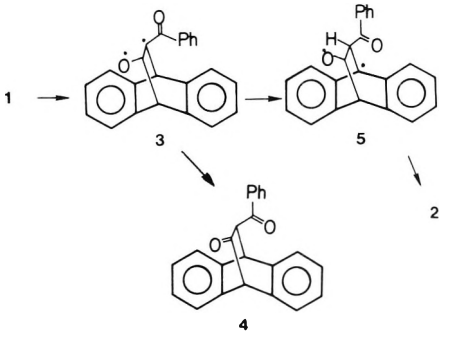
These data led to a tentative formulation of the product as **2**. This was further confirmed by a study of its ^1H and ^{13}C NMR spectra, which were as follows. ^1H NMR (220 MHz, $CDCl_3$) δ 8.64, d, 1 H, $C_{16}H$; 8.40, s, 1 H, $C_{15}H$; 7.45, m, 4 H, H at C_1, C_8, $C_{2'}$, and $C_{6'}$; 7.36, m, 4 H, H at C_{10}, $C_{3'}$, $C_{4'}$, and $C_{5'}$; 7.16, d, 2 H, C_4 H and C_5 H; 7.0, t, 2 H, C_2 H and C_7 H; 6.82, t,

2 H, C_3 H and C_6 H. Addition of D_2O caused sharpening of the doublet at δ 8.64 into a singlet, due apparently to a D_2O exchange with α-H to the carbonyl moieties causing decoupling of the aldehyde proton. Equilibration with water, however, caused broadening of the aldehyde proton. The ^1H NMR spectrum of the photoproduct in Me_2SO showed an apparent upfield shift of the aldehydic proton signal. This solvent effect was of the order of 60 Hz for a dilute sample. The remaining protons remained unaffected.

The ^{13}C NMR spectrum (Me_2SO-d_6) consisted of 191.7 (C_{17}), 164.5 (C_{16}), 138.7 ($C_{1'}$), 130.3 (C_9, $C_{4'}$), 129.5 ($C_{2'} = C_{6'}$), 129.4 ($C_{3'} = C_{5'}$), 128.6 (C_1, C_8), 127.6 ($C_{11} = C_{13}$), 127.3 ($C_{12} = C_{14}$), 125.4 (C_{10}), 125.0 ($C_4 = C_5$), 124.5 ($C_2 = C_7$), 124.1 ($C_3 = C_6$), and 115.0 ppm (C_{15}). The effect of the solvent (Me_2SO) may also be noted in the ^{13}C NMR spectrum where the aldehydic carbon signal appears at approximately −20 Hz from where normally expected. In addition, there is a broadening of the carbonyl C signals.

β-Keto aldehydes are reported to dissolve in Na_2CO_3 solution. The photoproduct (**2**) was allowed to stand with occasional shaking in a Na_2CO_3 solution; dissolution took place slowly.

The observed product (**2**) may arise from the common intermediate (**3**) via **5**. The diradical **3** is formed with a restricted configuration due to the bridge structure which allows for a small degree of rotational freedom thus permitting a higher degree of overlap with the bridgehead hydrogen ($C_{\beta'}$) over the groups at the C_β position. Migration of the bridgehead hydrogen would yield the biradical (**5**) which upon cleavage of



the C_β–C_γ bond can rearrange to the observed product. The major driving force to the latter would appear to be the energy gained in the formation of the aromatic nucleus. The alternative of a cleavage of the C_β–C_γ bond *before* migration of the hydrogen at the bridgehead cannot be excluded.

The restricted geometry of the intermediate **3** may also be responsible for the apparent lack of geometrical isomerization and formation of the 1,3-diketone **4** which in turn can lead to **2** and the formation of lactones[5] as secondary photoproducts.

Fragmentation of diketones (α diketones) leading to aromatic nuclei upon irradiation have been reported.[6] Related photorearrangements again leading to aromatic derivatives have been reported by Becker et al.[7] in the photolysis of spiro epoxy substituted 2,4-cyclohexadienone Diels–Alder dimer.

Experimental Section

Melting points were determined in a Thomas-Hoover melting apparatus and are uncorrected. Elemental analysis and molecular weight determinations of the product was done by Galbraith Laboratories Inc., Knoxville, Tenn. Deuterium exchange was carried out in a Varian T-60 (60 MHz), ^1H NMR was obtained in a Varian HR-220 (220 MHz) (Me_4Si was used as internal standard), and ^{13}C NMR was run in a Bruker HFX-10 spectrometer with Me_2SO-d_6 as internal standard. The irradiation source was a Hanovia 450-W medium-pressure mercury arc lamp.

7-Benzoyl-7,8-epoxydibenzobicyclo[2,2,2]octa-2,5-diene (1). The reaction of 7-benzoyldibenzobicyclo[2.2.2]octatriene with hydrogen peroxide in the presence of a base yields epoxy ketone **1**: mass spectrum M^+ 324; ir spectrum 1610, 1450, 1290 cm^{-1}; ^1H NMR δ 3.95, d, 1 H, J = 5 Hz, C_8 H; 4.65, d, 1 H, J = 5 Hz, C_4 H; 5.2, s, 1 H, C_1 H; 7.1–7.65, m, 11 H, Ar; 7.8–8.1, m, 2 H, ortho protons of -COPh.

Physical Data of Photoproduct 2. Electronic spectrum λ_{max} (pentane) nm (log ϵ) 388 (4.1), 368 (4.12), 349 (4.1), 332 (4.17), 320 (4.2), 254 (5.2), and 220 (4.37); ir spectrum 2850, 1490, 1445, (m, -C=C-), 3060 (w, aromatic C-H), and 735 cm^{-1} (aromatic C-H); mol wt 325 ± 5 (average of two determinations using benzene as solvent); mass spectrum fragmentation pattern *m/e* 324 (M^+), 219 (M − C_6H_5CO), 202 (M − C_6H_5CO − OH), 191 (M − C_6H_5CO − CO), 178 (anthracenyl moiety), 105 (C_6H_5CO), 77 (C_6H_5). Anal. Calcd: C, 85.18; H, 4.94. Found: C, 85.19; H, 4.93.

Registry No.—**1**, 59434-22-9; **2**, 59434-23-0; 7-benzoyldibenzobicyclo[2.2.2]octatriene, 57757-84-3.

References and Notes

(1) A Padwa, *Org. Photochem.*, **1**, 91 (1967); R. O. Kan, "Organic Photochemistry", McGraw-Hill, New York, N.Y., 1966, pp 129–140; J. A. Waters, Y. Kondo, and B. Witkop, *J. Pharm Sci.*, **61**, 321 (1972); J. J. Wuthrich, A. Siewinoki, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **56**, 239 (1973); K. Schaffner and O. Jeger, *Tetrahedron*, **30**, 1891 (1974).
(2) N. K. Saxena, Maya, and P. S. Venkataramani, *Indian J. Chem.*, **13**, 1075 (1975).
(3) K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1966, pp 42–43 and 65–69.
(4) "UV Atlas of Organic Compounds", Vol. II, Butterworths, London, 1966.
(5) T. Gibson, *J. Org. Chem.*, **39**, 845 (1974).
(6) J. Strating, B. Zwanenburg, A. Wagenaar, and A. C. Vading, *Tetrahedron Lett.*, 125 (1969).
(7) J.-D. Becker, B. Ruge, and T. Westlöf, *Tetrahedron Lett.*, 253 (1975).

Carbon Acids. 11. Acid Strengthening Alkyl Effects and Questionable Applications of the Taft Equation

Summary: Plots of σ^*_R vs. pK (in dimethyl sulfoxide for R = t-Bu, i-Pr, Et, and Me) in 9-R-X-fluorene systems gave ρ^*'s of −7.0, −7.3, and −7.6 for X = S, SO_2, and CH_2, respectively.

Sir: The relative polar effects of the alkyl substituents, Me, Et, i-Pr, and t-Bu have been the subject of considerable discussion. Ingold originally suggested that these groups possess inductive electron-releasing properties in the order t-Bu > i-Pr > Et > Me.[1] This order was later expressed quantitatively in terms of σ^* constants by Taft.[2] However, 15 years ago Ritchie pointed out that alkyl groups behave differently than groups containing heteroatoms with respect to "transmission coefficients", and showed that in many systems Taft correlations work as well when these four alkyl groups (and others) are assigned $\sigma^* = 0$, as when they are given the Taft values (σ^*'s = −0.3, −0.19, −0.1, and 0, respectively[2]).[3] Further doubt concerning the electron-releasing effect of these alkyl groups was raised by the discovery of Brauman and Blair that in the gas phase the acidities of the alcohols, t-BuOH, i-PrOH, EtOH, and MeOH, are in the reverse order to that found in solution.[4] Nevertheless, as pointed out by Shorter in a recent review of the Taft equation, "most physical organic chemists continue to believe that the electron-releasing properties of alkyl groups in aliphatic systems increase with chain length and branching and continue to use σ^* values as a measure of this".[5] For example, 9-substituted fluorenes have been shown to be particularly sensitive to alkyl effects, and Taft plots have been constructed based upon (a) rates of detritiation by NaOMe in MeOH (Et, Me, $PhCH_2$, CH_3OCH_2),[6] (b) rates of dedeuteration by NaOMe in MeOH (Et, Me, $PhCH_2$, $HOCH_2$, $MeOCH_2$; $\rho^* = 2.25$),[7] (c) equilibrium acidities in Me_2SO–H_2O (t-Bu, i-Pr, Et, Me, $PhCH_2$, Ph, CO_2Me; $\rho^* = 4.6$),[8] and (d) equilibrium acidities in cyclohexylamine (t-Bu, i-Pr, Et, Me, $PhCH_2$; $\rho^* = 4.547$).[9] Conclusions from these studies have been drawn concerning hyperconjugation of the CF_3 group,[6] the concertedness of E_2 eliminations,[7] the extent of carbanion formation in the transition state for detritiation,[8] and the nature of alkyl effects.[7,8] In this paper we present data to show that the order of these alkyl effects in 9-substituted fluorenes can be *reversed* by interposing an additional atom between R and the acidic site.

Examination of the equilibrium acidities in dimethyl sulfoxide of 9-alkylfluorenes gave the expected acidity order,[8,9] i.e., t-Bu < i-Pr < Et < Me, with about an equal sensitivity ($\rho^* = 6.7$, $r = 0.96$) as that observed in Me_2SO–H_2O or cyclohexylamine. On the other hand, for 9-alkylthiofluorenes the acidity increased as the size of the alkyl group increased, i.e., t-BuS > i-PrS > EtS > MeS. Plotting σ^*_R vs. pK for RS-fluorenes gave a better fit ($r = 0.99$) than for 9-alkylfluorenes; the ρ^* was slightly larger in size (7.0), but was, of course, *negative in sign*. Initially, we thought that this order was associated in some way with the high polarizability of the divalent sulfur atom, but further investigation showed that the Taft plots were also negative for 9-alkylsulfonylfluorenes ($\rho^* = -7.3$, $r = 0.98$) and even for 9-alkylmethylenefluorenes ($\rho^* = -7.6$, $r = 0.97$). In other words, by interposing S, SO_2, or CH_2 between R and the acidic site, the effect of increasing the size and branching of R in the fluorenyl anion has changed from deacidifying to acidifying.[10] For 9-R-fluorenes the increase in the destabilizing effect from Me to t-Bu amounts to about 2.7 kcal/mol, and for 9-RCH_2-fluorenes the increase in the stabilizing effect of R from Me to t-Bu is about 3.1 kcal/mol. If we assign the "normal" Taft σ^*'s to the RCH_2 substituents (i.e., Et, −0.10; Pr, −0.115; i-Bu, −0.125; *neo*-Pent, −0.165[2]), we find the correlation coefficient in the Taft plot to be excellent ($r = 0.99$), but ρ^* is ridiculously large and negative ($\rho^* = -36 \pm 4.5$). If all the alkyl points are included (Me, Et, i-Pr, i-Bu, t-Bu, neo-Pent) the Taft plot is chaotic ($\rho^* = 6.2 \pm 5.5$, $r = 0.45$). The pK's are summarized in Table I.

Table I. Equilibrium Acidities in Dimethyl Sulfoxide Solution for 9-R-X- and 9-R-Fluorenes [a]

Alkyl group	pK, 9-substituted fluorene			
	R	RCH_2	RS	RSO_2
Me	22.3_4	22.6	18.0	12.7_5
Et	22.6	22.2	17.5	12.3
i-Pr	23.2	21.6	16.9	11.7
t-Bu	24.3_5	20.3	15.9	10.5_5

[a] Average of values for two or more titrations using at least two indicators [see W. S. Matthews, et al., *J. Am. Chem. Soc.*, **97**, 7006 (1975) for the method used for these measurements]. The values using different indicators generally agreed to within ±0.05 pK units.

The observation of acid-strengthening alkyl effects in solution that increase in magnitude with increased size and branching of the alkyl group appears to be unique. We will reserve detailed comment on the nature of the factors determining alkyl effects pending additional experiments. A progressive increase in the relief of steric strain on forming the carbanion and/or a progressive increase in stabilization of the carbanion by polarization of the alkyl group are potential acid-strengthening effects that are being considered. The primary purpose of this communication, however, is to emphasize the dangers in drawing conclusions concerning polar effects from Taft plots which rely on alkyl points to construct the line.

Acknowledgment. We are grateful to the National Science Foundation (MPS74-12665) for support of this work and to Dennis K. Blood for the samples of 9-ethyl- and 9-isopropylfluorene.

References and Notes

(1) See C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1st ed, 1953, Chapter II, and references cited therein.
(2) R. W. Taft, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 13.
(3) C. D. Ritchie, *J. Phys. Chem.*, **65**, 2091 (1961); C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).
(4) J. Brauman and L. K. Blair, *J. Am. Chem. Soc.*, **92**, 5986 (1970).
(5) J. Shorter, *Adv. Linear Free Energy Relat.*, Chapter 2, 99–100 (1972).
(6) A. Streitwieser, A. P. Marchand, and A. H. Pudgjaatmaka, *J. Am. Chem. Soc.*, **89**, 693 (1967).
(7) R. A. More O'Ferrall and P. J. Warren, *J. Chem. Soc., Chem. Commun.*, 483 (1975); the $MeOCH_2$ point was not included in the plot.
(8) K. Bowden, A. F. Cockerill, and J. R. Gilbert, *J. Chem. Soc., B*, 179 (1970).
(9) A. Streitwieser, C. J. Chang, and D. M. E. Reuben, *J. Am. Chem. Soc.*, **94**, 5730 (1972); the t-Bu point was not included in the plot.

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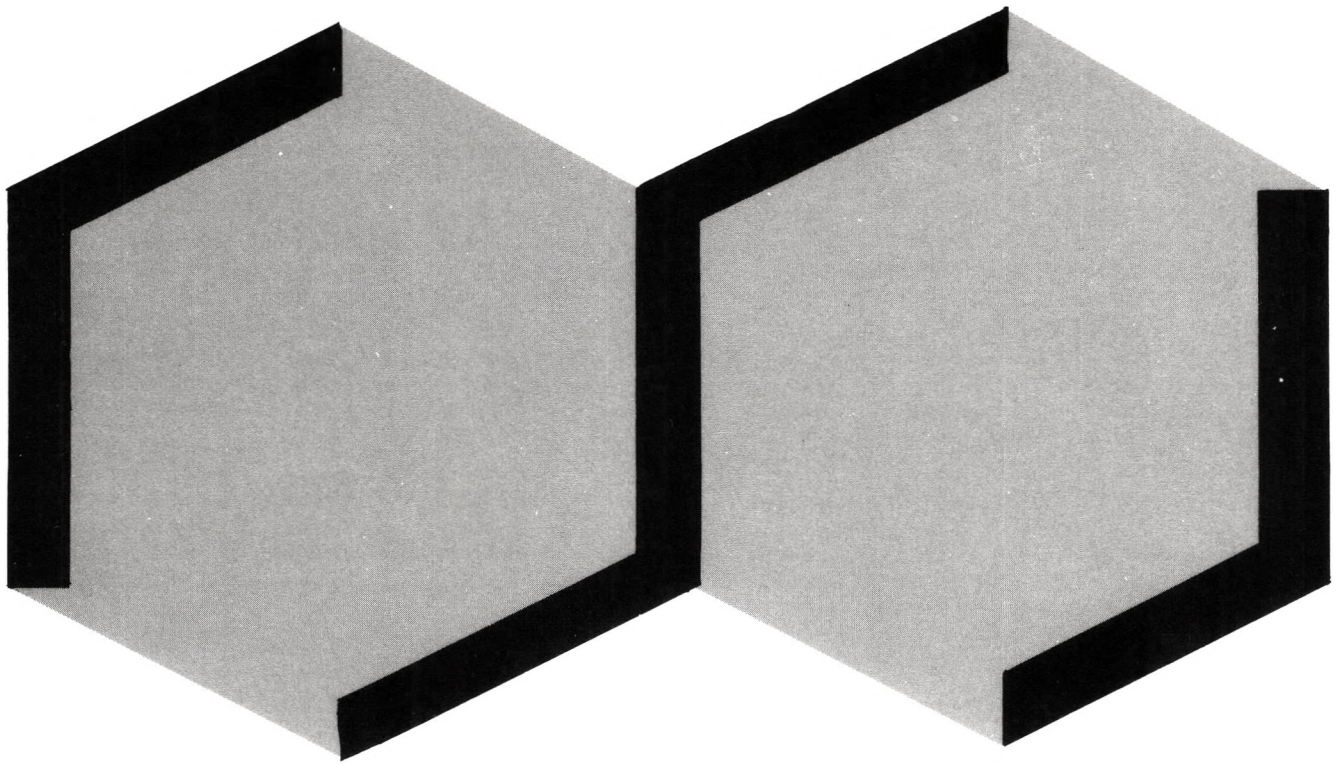

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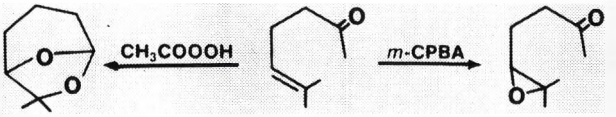
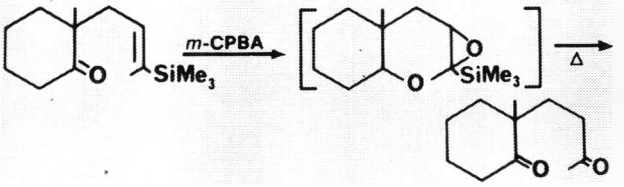
m-Chloroperoxybenzoic acid {m-CPBA}

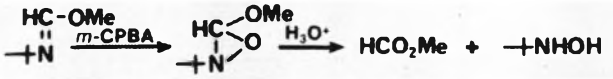
m*-Chloroperoxybenzoic acid** (m*-CPBA**) is a superior reagent for the selective epoxidation of isolated double bonds[1] and acid-sensitive olefins which produce rearranged products with other peracids.[2] Routine use of ***m*-CPBA** for the epoxidation of olefins has been reviewed.[3]



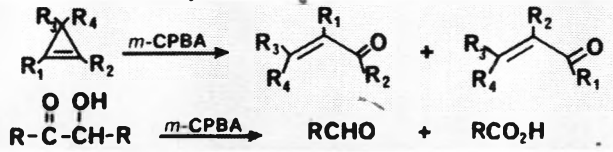
Trimethylsilyl vinyl systems react readily with ***m*-CPBA** to form trimethylsilyl epoxides which act as latent precursors to carbonyl groups.[4]



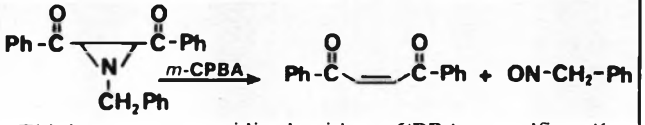
***m*-CPBA** oxidizes disubstituted acetylenes to oxirenes,[5,6] imines to oxazirines,[7] while iminoethers can be epoxidized and hydrolyzed to esters and hydroxylamines.[8]



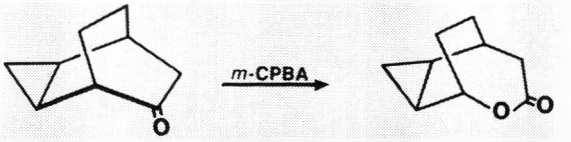
Cyclopropenes are oxidized to α,β-unsaturated ketones or aldehydes;[9] similarly, allenes[10] or α-hydroxy ketones[11] can be converted to aldehydes or acids.



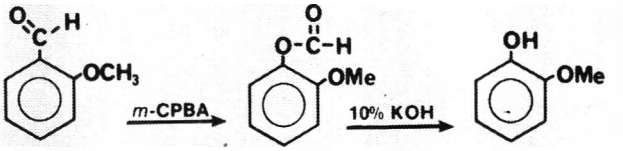
***m*-CPBA** has been used to convert primary amines to nitroalkanes,[12] nucleic acid components to their respective *N*-oxides[13] and *N*-substituted aziridines to *cis*-olefins.[14]



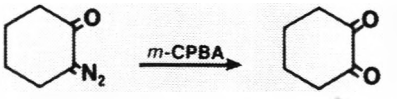
Thioketones are oxidized with ***m*-CPBA** to sulfines,[15] while alkyl mercaptans are converted to alkyl sulfinic acids.[16] ***m*-CPBA** is an excellent reagent for the Baeyer-Villiger oxidation of ketones to esters,[17] acid chlorides to alcohols,[18] and ketals to ortho esters.[19]



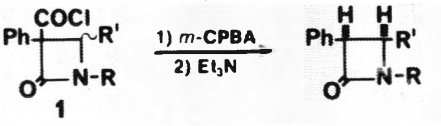
Various mono-, di- and trimethoxybenzaldehydes are oxidized with ***m*-CPBA** to formate esters which can be easily hydrolyzed to the corresponding methoxyphenols in high yield.[20]



α-Diketones are obtained in excellent yield from α-diazoketones by ***m*-CPBA** oxidation. For example, α-diazocyclohexanone is oxidized to 1,2-cyclohexanedione in 99% yield.[21]



An interesting and unique dehalocarbonylation reaction with ***m*-CPBA** provides *cis*-3-aryl-2-azetidinones , 2-aryl-β-lactam derivatives, from the β-lactam acid chloride **1**.[22]



1

***m*-CPBA** has also been used in the *p*-chlorination of *N*-methyl-*N*-acetylaniline, in the presence of $TiCl_4$.[23]

References:

(1) *J. Org. Chem.*, 38, 3145 (1973); **(2)** *ibid.*, 38, 2267 (1973); **(3)** *Reagents for Organic Synthesis*, 1, 1136 (1968); *Org. Syn.*, 49, 62 (1969); **(4)** *J. Amer. Chem. Soc.*, 96, 3682 (1974); **(5)** *ibid.*, 86, 4871 (1964); **(6)** *ibid.*, 92, 3826 (1970); **(7)** *ibid.*, 87, 4365 (1965); *ibid.*, 91, 6078 (1969); *ibid.*, 92, 4902 (1970); **(8)** *Tetrahedron Lett.*, 1807 (1973); **(9)** *J. Org. Chem.*, 39, 388 (1974); **(10)** *Acta Chem. Scand.*, 27, 1421 (1973); **(11)** *ibid.*, 27, 3365 (1973); **(12)** *J. Org. Chem.*, 31, 524 (1966); **(13)** *Biochemistry*, 8, 3059 (1969); *J. Chem. Soc., Perkin Trans. 1*, 333 (1973); **(14)** *Angew. Chem.*, 82, 395 (1970); **(15)** *J. Chem. Soc., Perkin Trans. 1*, 73, (1973); **(16)** *J. Org. Chem.*, 38, 4070 (1973); **(17)** *ibid.*, 40, 2070 (1975); **(18)** *ibid.*, 30, 3760 (1965); **(19)** *J. Chem. Soc. C*, 2934 (1968); **(20)** *J. Chem. Soc., Perkin Trans. 1*, 1353 (1974); **(21)** *J. Org. Chem.*, 39, 3295 (1974); (22) *Tetrahedron Lett.*, 1811 (1973); **(23)** *ibid.*, 2611 (1970);

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