VOLUME 40 MARCH 21, 1975 NUMBER 6 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

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JOCEAH (6) 667–818 (1975)
ISSN 0011-3263

THE JOURNAL OF Organic Chemistry®

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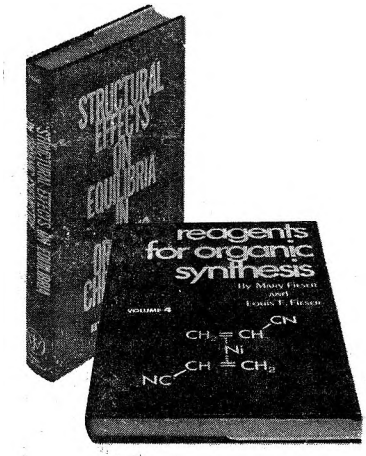

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Photochemical Transformations. XI. Photochemical and Thermal Rearrangements of Some β-Substituted Allylic Systems[1]

Stanley J. Cristol* and Roger P. Micheli

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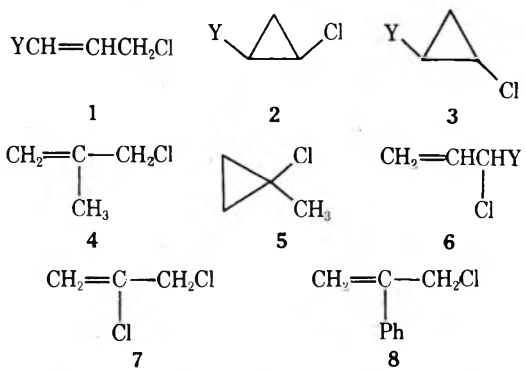
Received October 15, 1974

The photochemistry of β-chloro- and β-phenylcinnamyl and -crotyl chlorides has been investigated. These compounds, under both sensitized and direct irradiation, undergo cis–trans isomerizations and allylic rearrangements. The photostationary states contain substantial amounts of the thermally less stable secondary isomers. Sensitized irradiation of β-chlorocinnamyl *p*-toluenesulfonate and methanesulfonate also resulted in cis–trans isomerizations and rearrangements. Quantum yield and quenching results are reported and possible reaction mechanisms are discussed.

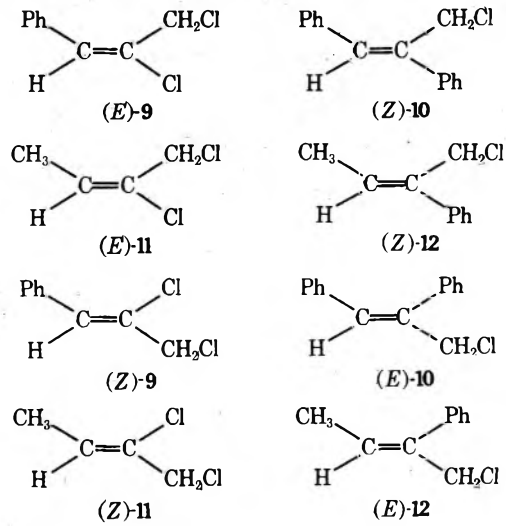
As reported earlier,[2] allyl chloride is readily transformed by triplet photosensitization to cyclopropyl chloride, and this photosensitized cyclization is a fairly general reaction. Thus, for example, crotyl chloride (1-Me) rearranges to a mixture of *cis*- and *trans*-2-chloro-1-methylcyclopropane (2-Me and 3-Me, respectively), cinnamyl chloride (1-Ph) to *trans*-2-chloro-1-phenylcyclopropane (3-Ph), and 2-methylallyl chloride (4) to 1-chloro-1-methylcyclopropane (5). α-Methylallyl chloride (6-Me), the allylic isomer of 1, also is photoisomerized to a mixture of 2-Me and 3-Me, and α-phenylallyl chloride (6-Ph) to 3-Ph, all *via* triplet intermediates.[2] Accompanying these 1,2-chlorine migration cyclizations is a generally somewhat faster allylic (1,3) migration. Thus, 1-Me and 6-Me suffer photosensitized isomerization to a mixture of the two, and 1-Ph is transformed to 6-Ph. Similar results were also noted for 1,3-dichloropropene (1-Cl) and 3,3-dichloropropene (6-Cl), which were also transformed to each other as well as photorearranged and cyclized to 2-Cl and 3-Cl.[2]



In view of these results, it was surprising that β-chloroallyl chloride (7) and β-phenylallyl chloride (8) were apparently inert to photosensitization, neither giving detectable amounts of the anticipated cyclopropane, when irradiated in acetone–acetonitrile solution with a Hanovia 450-W Model L lamp in thin-walled Pyrex tubes, the conditions used routinely for the photocyclization rearrangements.[2] As the allylic rearrangements of 7 and 8 (as well as cis–trans isomerizations) are degenerate processes and therefore hidden, we were unable to learn whether the photoinertness was complete or was limited to the 1,2-sigmatropic rearrangement–cyclization.

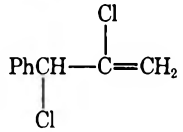
Results

We, therefore, have now prepared β-chlorocinnamyl chlorides (9) and β-phenylcinnamyl chlorides (10), and the analogous crotyl chlorides 11 and 12, where one can observe allylic rearrangements, cis–trans isomerizations, and allyl to cyclopropyl rearrangements, to the extent that any of these occur upon irradiation. Our preparative and isolation methods led to materials (which were used as reagents for photoreactions) which were 100% (*E*)-9 (β-chloro-*cis*-cinnamyl chloride), 100% (*E*)-10 (β-phenyl-*trans*-cinnamyl chloride), 98% (*E*)-11 (β-chloro-*cis*-crotyl chloride), and a



mixture of 17% of (*E*)-**12** (β-phenyl-trans-crotyl chloride) and 83% of (*Z*)-**12** (β-phenyl-*cis*-crotyl chloride).

Upon irradiation of these substances in acetonitrile–acetone solvent sensitizer, each was converted fairly rapidly toward a "photostationary" state of *E* and *Z* isomers. The compositions of these mixtures are described in the Experimental Section; in each case the cis cinnamyl or cis crotyl isomer predominated. Accompanying the cis–trans interconversion, but proceeding at about one-third the rate, was the photochemical allylic rearrangement. Thus, irradiation of a 0.5 *M* solution of **9** for 72 hr led to complete transformation to the allylic isomer, β-chloro-α-phenylallyl chloride (**13**), without any allyl to cyclopropyl rearrangement to **14** being observed, even on longer irradiation. Irradiation of



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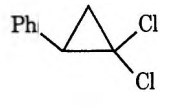

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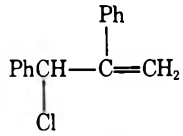

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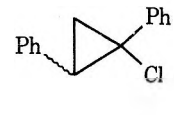

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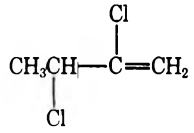
13 gave neither cyclization to **14** nor formation of the primary chlorides **9** upon irradiation, within our ability to detect them by pmr analysis. Of possible synthetic importance is the fact that **13** is the "stable" isomer in the **9** ↔ **13** photoequilibration, while in a ferric chloride catalyzed ground-state equilibration **13** is converted completely to **9**. Thus the photochemical isomerization is a useful synthetic procedure for the secondary isomer **13** from the readily available **9**.

Similarly, irradiation of β-phenylcinnamyl chloride (**10**) led to a mixture rich (79%) in the secondary allylic isomer **15**, while ferric chloride catalyzed treatment gave substantially pure primary isomer **10**. The ground-state results on the cinnamyl systems are consistent with those anticipated,[3] while the photochemical results (secondary isomer more photo-"stable") are consistent with those observed earlier[2b] with cinnamyl chloride itself. We rationalize these results on the basis that the more highly conjugated primary isomers **9** and **10** have lower singlet energies and therefore probably lower triplet energies than their secondary isomers **13** and **15**, and that the photoisomerization proceeds to the less conjugated system. Put another way, the triplets of **13** and **15** might be quenched by **9** and **10**, respectively, so that the **9** to **13** reaction (and that of **10** to **15**) would be expected to be more important than the corresponding reverse reactions. An obvious alternative is that energy transfer from sensitizer to the primary isomer is more efficient than that to the secondary isomer.

In the crotyl systems, irradiation of either **11** or its isomer **17** led to a photostationary state mixture containing 70% of **11** and 30% of **17**, while that of either **12** or **18** gave a



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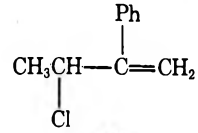

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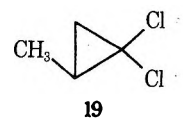

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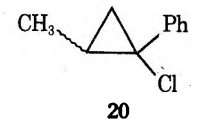

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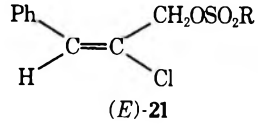
mixture containing 83% of **12** and 17% of **18**. The corresponding ground-state equilibrations gave mixtures comprising 85% of **11** and 15% of **17** and 76% of **12** and 24% of **18**, respectively.

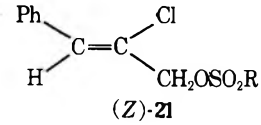
In none of the irradiations was any of the cyclopropanes **14**, **16**, **19**, or **20** detected. In order to test the possibility that the cyclopropanes might be formed, but somehow be unstable to the reaction conditions, **14** and **19** were prepared and irradiated in acetone–acetonitrile (λ >270 nm). Both substances were completely stable.

Our previous results[2] had indicated that all of the processes investigated were reactions involving triplet sensitization, but Bohlmann and his coworkers[4] have reported that a number of allylic chlorides conjugated with alkynyl groups do undergo nonstereospecific photocyclization–rearrangements to alkynylcyclopropyl chlorides upon direct irradiation in nonpolar solvents, apparently *via* singlet intermediates. We thought that perhaps **9** and **10**, which have conjugation of the allylic double bond with aromatic rings or with an aromatic ring and a chlorine atom, might similarly undergo cyclization upon direct irradiation. However, a 120-hr irradiation of (*E*)-**9** in hexane at 300 nm produced no cyclopropane, but only slow cis–trans isomerization and allylic rearrangement to give 79% of (*E*)-**9**, 9% of (*Z*)-**9**, and 12% of **13**. A similar irradiation of (*E*)-**10** produced 25% of the allylic isomer **15**, as well as 15% of (*Z*)-**10**, and again no cyclopropane was formed. It is of interest that Bohlmann did not observe allylic rearrangement in his work.[4]

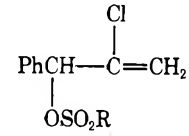
Cookson and coworkers[5] have reported that cinnamyl benzoate and acetate photoisomerize to the secondary α-phenylallyl esters with cinchonidine sensitizers. The reaction with the benzoate ester has also been shown[2b] to proceed with acetone sensitization, but cyclization rearrangement was not observed. Sulfonate esters of allylic alcohols are notoriously unstable,[6] but, owing to the β-chlorine atom, the thermal reactivity of esters of β-chlorocinnamyl alcohol might be expected to be reduced. Both the methanesulfonate ester ((*E*)-**21**-Me) of β-chloro-*cis*-cinnamyl alcohol and the *p*-toluenesulfonate ester ((*E*)-**21**-Tl) were



(*E*)-**21**



(*Z*)-**21**



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Me, R = CH_3
Tl, R = $C_6H_4CH_3$-*p*

prepared and were reasonably stable at room temperature. Irradiation of these esters in acetone–acetonitrile gave a rapid cis–trans photoisomerization to a mixture containing 33–35% of the (*Z*)-**21** species, and a slower photoallylic rearrangement. After 70 hr, **21**-Me was converted to 23% of **22**-Me, and **21**-Tl to about 53% of **22**-Tl.[7] No cyclopropane was noted in the irradiation product.[8]

Mechanistic Studies. Although there are examples of photochemical 1,3 (allylic) migrations of a large variety of groups including acyl,[9] alkyl,[10] allyl,[5] phenyl,[11] benzyl,[12] vinyl,[11b,13] boron,[14] and halogen,[2,4] mechanistic details of many of these are unclear. As the allylic rearrangement of **9** and **10** proceeded upon direct irradiation as well as in solutions containing acetone, we began our quantum yield and

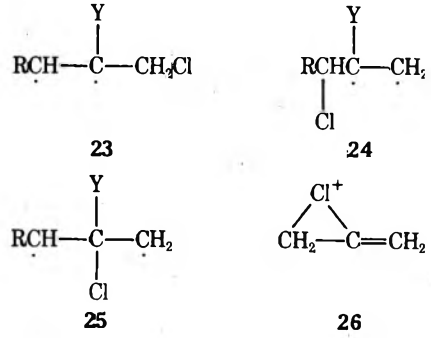
quenching studies with these compounds. In 0.2 *M* allyl chloride solutions in acetonitrile, the quantum yield for rearrangement of **9** to **13** was found to be 0.016 (a Rayonet photoreactor with 300-nm lamps was used for all quantitative studies) and for that of **10** to **15** was 0.025. Quenching experiments for the **9** → **13** transformation with 1,3-cyclohexadiene gave a Stern–Volmer plot with a slope of 4 (quantum yield reduced by 50% at 0.5 *M* diene). As this low value implies either that the triplet state of the diene is higher in energy than that of the triplet state of **9** or that the singlet state is being quenched,[15] we then looked at similar quenching of acetone solutions of **9**. Our results clearly exclude the first alternative. Thus, the quantum yield for **9** → **13** interconversion of a 0.25 *M* solution of **9** in 20% acetone in acetonitrile was found to be 0.24. The reaction was half-quenched with diene concentrations of about 0.002 *M*. A plot of ϕ_0/ϕ *vs.* diene concentration[16] was linear out to about 0.1 *M* diene, but at higher diene concentrations the slope fell off rapidly. This suggests that the allylic rearrangement proceeds *via* both singlet and triplet states of **9**, with the reaction involving the triplet being substantially more efficient. The data also show that, in the direct irradiation process (in acetonitrile), the singlet produced by direct light absorption proceeds to product without crossing to the triplet, and suggest, as well, that (in acetone) about 7% of the product comes from direct absorption of light by **9** and subsequent product formation, and 93% arises *via* acetone triplets. In direct irradiation, cis–trans isomerization occurs slowly relative to that in the triplet process, and although such a process might be occurring from the singlet state, as in stilbene photochemistry,[17] we cannot rule out the possibility of isomerization arising as a consequence of the photoallylic rearrangement equilibration.

Similarly ϕ for the unsensitized transformation of **10** to **15** (in acetonitrile) was found to be 0.025, while that in acetone–acetonitrile was found to be 0.086 (0.25 *M* **10**). Quenching of the sensitized reaction gave a second-order Stern–Volmer[16] plot which was linear with a slope of 53 at low concentrations (2×10^{-5} to 0.02 *M*) of diene and which fell off at higher concentrations of diene to a line with almost zero slope. Thus again, both singlet and triplet noninterconvertible product progenitors seem required by the data with about one-third of the reaction in the solvent/sensitizer system used proceeding *via* the singlet and two-thirds *via* the triplet in this case. These values presumably reflect relative absorbances of **9** and/or **10** and acetone. Use of a sensitizer such as acetophenone and longer wavelength light would probably give increased efficiencies for the sensitized reaction, as it would cut down on direct irradiation processes, and thus give better "Stern–Volmer" plots. Finally, quantum yields for the sensitized transformations of **11** to **17** and of **12** to **18** were found to be 0.073 and 0.042, respectively, and quenching of the latter transformation gave a linear "second-order" Stern–Volmer plot with a slope of 250 over the range 0.0002–0.07 *M* diene.

Discussion

In the previous papers on related rearrangements from this laboratory,[2] a number of detailed mechanistic paths were proposed which were consistent with the data presented. One of these involved homolytic cleavage of the allyl chloride carbon–chlorine bond, followed by recombination. This certainly is a possibility here, but is somewhat unattractive in view of our failure to see other products of free-radical intermediates. Thus, while the allylic radical is relatively unreactive, we would expect to find evidence for its dimerization or for its combination with radicals formed by abstraction of hydrogen atoms from solvent by chlorine atoms[2b] or by addition of chlorine atoms to the allylic double bond.[18]

A second alternative involved the intermediacy of a triplet biradical, and in the present cases might include the corresponding singlet biradicals as well. It was suggested that such biradicals **23** might be anticipated to suffer 1,3-sigmatropic rearrangement to radicals **24** followed by (or in



23 **24**

25 **26**

concert with) double bond reconstitution to give allylic isomers or a 1,2 rearrangement to give 1,3-biradicals **25** followed by (or in concert with) ring closure to give cyclopropane. The stereoselectivity noted in the cyclopropane formation[2b,19] set serious boundaries on the latter path. If such biradicals are indeed intermediates, one must explain why the formation of **25** proceeds efficiently ($\phi \sim 0.1$) when Y is hydrogen or alkyl,[2b,18c] with R variable, but not at all when Y is chlorine or phenyl. There is, of course, conjugation energy lost in the **23** to **25** transformation, but this is true as well, although to a lesser extent,[20] for the Y = alkyl cases. The fact that the sulfonate esters show reactions similar to those of the chlorides makes the radical recombination or biradical paths less attractive, assuming that reaction paths identical with those of the chlorides are traversed.

It has also been suggested[2] that the rearrangements involve carbenium ion–anion pairs in which the cation is of the ground electronic state, but vibrationally excited. Olah[22] has shown that 2-chloroallyl cation does not exist in superacid solution, but instead the isomer **26** is stable. Although an analogous situation does not obtain with methyl-substituted 2-chloroallyl cations,[22] species related to **26** may exist in our systems and may fail to rearrange to chlorocyclopropane upon attack by chloride ion. Similar effects might be expected for 2-phenylallyl cations, but not for 2-alkylallyl ones. The photoisomerization of the sulfonate esters **21** to **22** also seems consistent with the carbenium ion process, but the possibility of a concerted [3.3] sigmatropic (photo-Claisen) or of a [1.3] sigmatropic rearrangement also remains. Labeling experiments and stereochemical studies are needed to define these reactions better.

Experimental Section

Proton magnetic resonance spectra were obtained with a Varian A-60A spectrometer. Infrared spectra were run in carbon tetrachloride, using either a Perkin-Elmer Model 337 or Model 137 spectrophotometer. Mass spectra were obtained on a Varian MAT Model CH-7 spectrometer. Analyses of some experiments were performed by gas chromatography (gc) using a Varian Aerograph Model A-90 P-3 instrument. Preparative separations were carried out on an Aerograph Autoprep Model A-700 gas chromatograph. Irradiations were performed using one of two procedures. Method A involved irradiation of 0.5 *M* solutions of each compound in question in acetone-d_6–acetonitrile-d_3 (1:4, v/v, unless specified otherwise) in thin-walled Pyrex tubes (nmr probes) following deaeration with nitrogen for 1 hr at −20°. For these irradiations, a Hanovia 450-W mercury arc lamp (Engelhardt-Hanovia, Inc., Newark, N.J., Model L-679A-36) inserted into a water-cooled quartz-immersion probe was employed. Method B was used for quantitative experiments and involved degassing 3.0-ml sample solutions in

preconstricted 13 × 100 mm Pyrex test tubes on a vacuum line with five freeze–pump–thaw cycles and sealing at pressures less than 10^{-5} Torr. The sealed tubes for any single experiment were irradiated in parallel with cyclopentanone actinometer solutions[23] in a merry-go-round photolysis apparatus, using a Rayonet RPR-208 photochemical reactor equipped with 300-nm lamps (The New England Ultraviolet Co., Middletown, Conn.). All quantum yields obtained by these experiments were corrected for back reaction.[24]

(*E*)-β-Phenylcinnamyl alcohol was synthesized as described elsewhere.[25]

(*E*)-β-Phenylcinnamyl chloride (10) was synthesized using a general procedure devised by Collington and Meyers,[26] and exhibited properties identical with those previously reported:[25] pmr (CCl_4) δ 7.02–7.23 (m, 10 H), 6.70 (t, J = 0.5 Hz, 1 H), 4.29 (d, J = 0.5 Hz, 2 H).

2,3-Diphenyl-3-chloropropene (15) was prepared from the alcohol using a general method described by Young.[27] Bulb-to-bulb distillation at reduced pressure in a "Kugel Rohr Oven" (131° (2.8 Torr)) gave a 65% yield of **15**: pmr (CCl_4) δ 6.8–7.1 (m, 10 H), 5.88 (s, 1 H), 5.23 (d, J = 0.5 Hz, 1 H), 5.19 (d, J = 0.5 Hz, 1 H).

Anal. Calcd for $C_{15}H_{13}Cl$: C, 78.77; H, 5.72. Found: C, 78.76; H, 5.78.

(*E*)-β-Chlorocinnamyl alcohol was prepared as described elsewhere.[28]

(*E*)-β-Chlorocinnamyl chloride (9) was obtained from the alcohol as previously described for β-phenylcinnamyl chloride. Distillation at reduced pressure (94–95° (2.5 Torr); lit.[29] 109–110° (4 Torr)) resulted in a 70% yield of **(*E*)-9**: pmr (CCl_4) δ 6.95–7.95 (m, 5 H), 6.35 (s, 1 H), 3.88 (s, 2 H).

3-Phenyl-2,3-dichloropropene (13) was prepared as previously described for 2,3-diphenyl-3-chloropropene. Purification by bulb-to-bulb distillation at reduced pressure (89–90° (1.8 Torr)) resulted in a 43% yield of **13**: pmr (CCl_4) δ 6.95–7.30 (m, 5 H), 5.52 (s, 1 H), 5.50 (d, J = 2.0 Hz, 1 H), 5.22 (d, J = 2.0 Hz, 1 H).

Anal. Calcd for $C_9H_8Cl_2$: C, 57.78; H, 4.31. Found: C, 57.68; H, 4.44.

(*E*)-β-Chlorocrotyl alcohol was prepared as described elsewhere.[28]

(*E*)-β-Chlorocrotyl chloride (11) was prepared from the alcohol as described for β-phenylcinnamyl chloride. Purification was accomplished by gc (25% Carbowax 20M on Chromosorb P at 150°, 12 ft × 0.375 in. Al column). The pure dichloride exhibited properties identical with those previously reported:[30] pmr (CCl_4) δ 5.89 (q, J = 6.5 Hz, 1 H), 4.08 (d, J = 0.5 Hz, 2 H), 1.63 (d of d, J = 6.5, and 0.5 Hz, 3 H).

2,3-Dichloro-1-butene (17) was prepared as described for 2,3-diphenyl-3-chloropropene. Purification was accomplished by gc (25% Carbowax 20M on Chromosorb P at 150°, 12 ft × 0.375-in. Al column): pmr (CCl_4) δ 5.14 (d, J = 1.5 Hz, 1 H), 4.85 (d, J = 1.5 Hz, 1 H), 4.37 (q, J = 6.5 Hz, 1 H), 1.21 (d, J = 6.5 Hz, 3 H).

Anal. Calcd for $C_4H_6Cl_2$: C, 36.68; H, 4.62. Found: C, 36.47; H, 4.73.

β-Phenylcrotonaldehyde was prepared as described elsewhere.[31]

β-Phenylcrotyl alcohol was prepared from the aldehyde as described for β-phenylcinnamyl alcohol. Distillation at reduced pressure (101–102° (2.8 Torr)) gave a mixture of the two isomeric alcohols, which was used in the next step without further characterization.

β-Phenylcrotyl chloride (12) was prepared as described for β-phenylcinnamyl chloride. Distillation at reduced pressure gave a mixture of Z and E isomers (83:17, respectively): pmr (CCl_4) δ 7.15 (m, 5 H), 5.76 (q, J = 6.0 Hz, 1 H), 4.14 (d, J = 1.0 Hz, 2 H), 1.28 (d of d, J = 6.0 and 1.0 Hz, 3 H).

Anal. Calcd for $C_{10}H_{11}Cl$: C, 72.04; H, 6.66. Found: C, 72.19; H, 6.74.

3-Chloro-2-phenyl-1-butene (18) was prepared as described for 2,3-diphenyl-3-chloropropene and was obtained in a 40% yield by distillation at reduced pressure (96–98° (2.5 Torr)): pmr (CCl_4) δ 7.25 (m, 5 H), 5.35 (d, J = 0.5 Hz, 1 H), 5.21 (d, J = 0.5 Hz, 1 H), 4.95 (q, J = 7.0 Hz, 1 H), 1.47 (d, J = 7.0 Hz, 3 H).

Anal. Calcd for $C_{10}H_{11}Cl$: C, 72.04; H, 6.66. Found: C, 72.12; H, 6.75.

1,1-Dichloro-2-phenylcyclopropane[32] (14) and **1,1-dichloro-2-methylcyclopropane[33] (19)** were synthesized as described elsewhere.

Irradiation of β-Chlorocinnamyl Chloride ((*E*)-9) and 3-Phenyl-2,3-dichloropropene (13) in Acetone–Acetonitrile. β-Chlorocinnamyl chloride (0.094 g, 0.5 mmol) was diluted with 0.8 ml of acetonitrile-d_3 and 0.2 ml of acetone-d_6 and placed in a Pyrex nmr tube. The sample was handled as outlined in method A, and irradiated for a total of 100 hr, with the reaction progress monitored by pmr. After 6 hr of irradiation, cis–trans isomerization became evident and a photostationary mixture composition of 64% of **(*E*)-9** and 36% of **(*Z*)-9** was determined. After 76 hr no further change in the pmr spectrum was noted, and it was determined that 100% conversion to the allylic isomer **13** had occurred. No evidence of cyclization was observed.

Similar treatment of 3-phenyl-2,3-dichloropropene (**13**) resulted in no change in the pmr spectrum, even after 100 hr of irradiation.

Ferric Chloride Isomerization of β-Chlorocinnamyl Chloride (9) and 3-Phenyl-2,3-dichloropropene (13). 3-Phenyl-2,3-dichloropropene (1.0 g, 5.3 mmol) was diluted with 4.0 ml of spectroquality cyclohexane, to which a trace of ferric chloride has been added. The solution was heated at reflux for 20.5 hr, after which pmr analysis indicated 100% conversion to the primary isomer **9** had occurred.

Similar treatment of β-chlorocinnamyl chloride (**9**) led to no detectable formation of the secondary isomer **13**, even after 23 hr of reflux.

Irradiation of β-Phenylcinnamyl Chloride ((*E*)-10) and 2,3-Diphenyl-3-chloropropene (15) in Acetone–Acetonitrile. β-Phenylcinnamyl chloride (0.115 g, 0.5 mmol) was diluted with 0.3 ml of acetonitrile-d_3 and 0.2 ml of acetone-d_6 and placed in a Pyrex nmr tube. The sample was handled as outlined in method A, with the progress of the reaction being monitored by pmr. After 3 hr of irradiation cis–trans isomerization became evident, and a photostationary mixture composition of 6% of **(*E*)-10** and 94% of **(*Z*)-10** was determined after 12 hr. At the end of 23.5 hr, no further changes in the pmr spectrum could be detected and the product mixture was determined to consist of 27% of **10** and 73% of **15**.

Similar treatment of 2,3-diphenyl-3-chloropropene (**15**) produced a mixture of 28% of **10** and 72% of **15**.

Ferric Chloride Isomerization of β-Phenylcinnamyl Chloride (10) and 2,3-Diphenyl-3-chloropropene (13). 2,3-Diphenyl-3-chloropropene (1.0 g, 4.4 mmol) was treated as previously described for 3-phenyl-2,3-dichloropropene. After the solution was heated at reflux for 24 hr, pmr analysis indicated 100% conversion to the primary isomer **10** had taken place.

Similar treatment of **10** led to no detectable formation of the secondary isomer **13**.

Irradiation of β-Chlorocrotyl Chloride ((*E*)-11) and 2,3-Dichloro-1-butene (12) in Acetone–Acetonitrile. β-Chlorocrotyl chloride (0.066 g, 0.5 mmol) was diluted with 0.8 ml of acetonitrile-d_3 and 0.2 ml of acetone-d_6. The sample was then handled as outlined in method A. Pmr analysis indicated that cis–trans isomerization had reached a photosteady composition of 78% of **(*Z*)-11** and 22% of **(*E*)-11** after 12 hr. After 96 hr, no further changes in the pmr spectrum were detected, and it was determined that the product mixture consisted of 30% of **17** and 70% of **11**.

Similar treatment of **17** produced an identical mixture.

Ferric Chloride Isomerization of β-Chlorocrotyl Chloride (11) and 2,3-Dichloro-1-butene (17). β-Chlorocrotyl chloride (1.0 g, 7.6 mmol) was treated as previously described for 3-phenyl-2,3-dichloropropene. After the solution was heated at reflux for 24 hr, pmr analysis indicated that the product mixture consisted of 85% of **11** and 15% of **17**.

Similar treatment of **17** produced an identical mixture.

Irradiation of β-Phenylcrotyl Chloride (12) and 2-Phenyl-3-chloro-1-butene (18). β-Phenylcrotyl chloride (0.083 g, 0.5 mmol) was diluted with 0.8 ml of acetonitrile-d_3 and 0.2 ml of acetone-d_6, and the solution was handled as outlined in method A. Cis–trans isomerization was detectable by pmr analysis after 2 hr, leading to a photostationary mixture of 68% **(*Z*)-12** and 32% of **(*E*)-12** after 9.5 hr. After irradiation for 40 hr, no further changes in the pmr spectrum were detected, and it was determined that the product mixture consisted of 83% of **12** and 17% of **18**.

Similar treatment of **18** produced a mixture containing 79% of **12** and 21% of **18**.

Ferric Chloride Isomerization of β-Phenylcrotyl Chloride (12) and 2-Phenyl-3-chloro-1-butene (18). β-Phenylcrotyl chloride (1.0 g, 6.1 mmol) was treated as previously described for 3-phenyl-2,3-dichloropropene. Analysis by pmr indicated that the product mixture consisted of 76% of **12** and 24% of **18**.

Similar treatment of the allylic isomer **18** led to an identical product mixture.

Irradiation of 1,1-Dichloro-2-methylcyclopropane (19) and 1,1-Dichloro-2-phenylcyclopropane (14) in Acetone–Acetonitrile. A solution of 1,1-dichloro-2-methylcyclopropane (0.094 g, 0.5 mmol) in 0.8 ml of acetonitrile-d_3 and 0.2 ml of acetone-d_6 was

treated as described for the preceding allylic halides. No observable change in the pmr spectrum could be detected, even after 120 hr of irradiation. 1,1-Dichloro-2-phenylcyclopropane (14), treated similarly, produced the same result.

Direct Irradiation of β-Phenylcinnamyl Chloride (10) and β-Chlorocinnamyl Chloride (9) in Hexane. β-Phenylcinnamyl chloride (0.115 g, 0.5 mmol) was diluted with 1.0 ml of hexane and placed in a Pyrex nmr tube, and the sample was handled as described in method A. After irradiation for 120 hr, pmr analysis indicated that the product mixture contained 25% of **15** and 75% of **10** (15% of (*Z*)-**10** and 85% of (*E*)-**10**).

Similar treatment of **9** produced a mixture containing 12% of **13** and 88% of **9** (9% (*Z*)-**9** and 91% (*E*)-**9**).

β-Chlorocinnamyl *p*-toluenesulfonate (21-Tl), mp ~15°, was prepared according to the general procedure of Marvel and Sekera.[34] The compound obtained was stable in solutions kept below room temperature. For this reason, the compound was not further characterized: pmr (acetone-d_6) δ 7.0–7.9 (m, 9 H), 6.7 (s, 1 H), 4.15 (s, 2 H), 2.1 (s, 3 H).

β-Chlorocinnamyl methanesulfonate (21-Me), mp ~3°, was prepared according to the general method of Marvel and Sekera.[35] For the same reason cited above, this compound was not further characterized: pmr (acetone-d_6) δ 7.2–7.8 (m, 5 H), 6.8 (s, 1 H), 4.2 (s, 1 H), 3.0 (s, 3 H).

Irradiation of β-Chlorocinnamyl *p*-Toluenesulfonate (21-Tl) and Methanesulfonate (21-Me) in Acetone–Acetonitrile. β-Chlorocinnamyl *p*-toluenesulfonate (0.161 g, 0.5 mmol) was dissolved in 0.8 ml of acetonitrile-d_3 and 0.2 ml of acetone-d_6, taking care that the solution was kept below room temperature, and the sample was handled as described in method A. Irradiation was performed in a water bath held between 12 and 15° to minimize thermal reactions.[36] After 70 hr of irradiation, it was determined by pmr analysis that 53% conversion to the allylic isomer (**22-Tl**) had taken place.

Similar treatment of the methanesulfonate (**21-Me**) resulted in a 23% conversion to the allylic isomer (**22-Me**), as determined by pmr analysis.

Quantum Yield Determination for β-Chlorocinnamyl Chloride (9) and β-Phenylcinnamyl Chloride (10) in Acetonitrile (Direct). β-Chlorocinnamyl chloride (0.919 g, 4.91 mmol) was diluted to 25.0 ml with acetonitrile. Four 3.0-ml aliquots were added to four Pyrex test tubes and the samples were handled as outlined in method B. Work-up following irradiation consisted of solvent removal and dilution of the product mixture with 1.0 ml of a 0.2 *M* solution of cyclohexane (internal standard) in carbon tetrachloride. After 47.5 hr of irradiation, the first tube contained 3.6% of **13** (ϕ = 0.014). After 72 hr of irradiation, the second tube contained 6.1% of **13** (ϕ = 0.018). After 144 hr of irradiation, the third tube contained 9.1% of **13** (ϕ = 0.018). After 219 hr of irradiation, the fourth tube contained 15.9% of **13** (ϕ = 0.015).

β-Phenylcinnamyl chloride (**10**) was treated similarly. After 49 hr of irradiation, the product mixture contained 5.1% of **15** (ϕ = 0.025). After 100 hr of irradiation, the product contained 9.6% of **15** (ϕ = 0.025).

Quantum Yield Determination of β-Phenylcinnamyl Chloride (10) and β-Chlorocinnamyl Chloride (9) in Acetone–Acetonitrile. β-Phenylcinnamyl chloride (0.363 g, 1.59 mmol) was diluted to 6.0 ml with acetone–acetonitrile solution, and this was divided between two preconstricted Pyrex test tubes. The samples were then handled as outlined in method B. After 49.1 hr of irradiation and work-up as described above, one of the tubes contained 17.4% of **15** (ϕ = 0.087), while the other contained 17.2% of **15** (ϕ = 0.086).

β-Chlorocinnamyl chloride (**9**) was treated similarly, and after 19 hr of irradiation, one of the tubes contained 10.9% of **13** (ϕ = 0.245), while the other contained 10.7% of **13** (ϕ = 0.242).

Quenching of Rearrangement of β-Chlorocinnamyl Chloride (9) by 1,3-Cyclohexadiene in Acetonitrile (Direct). β-Chlorocinnamyl chloride (1.14 g, 6.06 mmol) was diluted to 10.0 ml with acetonitrile, and 2.0-ml aliquots of this solution were placed in five preconstricted Pyrex test tubes. To these were added, respectively, 1.0-ml aliquots of 0.06, 0.006, 0.0006, and 0.0 *M* solutions of 1,3-cyclohexadiene in acetonitrile. The samples were then handled as outlined in method B. After irradiation for 150 hr, the following results were obtained: [diene] = 0.0 *M*, 7.8% of **13** (ϕ = 0.018); [diene] = 0.2 *M*, 9.5% of **13** (ϕ = 0.022); [diene] = 0.02 *M*, 8.2% of **13** (ϕ = 0.019); [diene] = 0.002 *M*, 6.5% of **13** (ϕ = 0.015); [diene] = 0.0002 *M*, 6.4% of **13** (ϕ = 0.015).

Quenching of Rearrangement of β-Chlorocinnamyl Chloride (9) by 1,3-Cyclohexadiene in Acetone–Acetonitrile. β-Chlorocinnamyl chloride (2.83 g, 14.0 mmol) was diluted to 20.0 ml with acetone–acetonitrile solution, and 2.0-ml aliquots of this were placed in seven preconstricted Pyrex test tubes. To these were added, respectively, 1.0-ml aliquots of 3.0, 0.3, 0.03, 0.003, 0.0003, 3×10^{-5}, and 0.0 *M* solution of 1,3-cyclohexadiene in acetone–acetonitrile. The samples were then handled as outlined in method B. After irradiation for 28.3 hr and work-up as described before, the following results were obtained: [diene] = 0.0 *M*; 16.4% of **13** (ϕ = 0.25); [diene] = 1.0 *M*, 1.1% of **13** (ϕ = 0.017); [diene] = 0.1 *M*, 1.0% of **13** (ϕ = 0.015); [diene] = 0.01 *M*, 3.1% of **13** (ϕ = 0.046); [diene] = 0.001 *M*, 10.0% of **13** (ϕ = 0.154); [diene] = 0.0001 *M*, 15.6% of **13** (ϕ = 0.229); [diene] = 10^{-5} *M*, 16.0% of **13** (ϕ = 0.244).

Quenching of Rearrangement of β-Phenylcinnamyl Chloride (10) with 1,3-Cyclohexadiene in Acetone–Acetonitrile. β-Phenylcinnamyl chloride (0.740 g, 3.24 mmol) was diluted to 10.0 ml with acetone–acetonitrile solution, and 2.0-ml aliquots of this were placed in five preconstricted Pyrex test tubes. To these were added, respectively, 1.0-ml aliquots of 3.0, 0.3, 0.2, 0.1, and 0.0 *M* 1,3-cyclohexadiene in acetone–acetonitrile. The samples were then handled as outlined in method B. After irradiation for 50 hr and work-up as previously described, the following results were obtained: [diene] = 0.0 *M*, 17.6% of **15** (ϕ = 0.086); [diene] = 1.0 *M*, 6.1% of **15** (ϕ = 0.026); [diene] = 0.1 *M*, 5.9% of **15** (ϕ = 0.025); [diene] = 0.067 *M*, 7.5% of **15** (ϕ = 0.033); [diene] = 0.033 *M*, 10.1% of **15** (ϕ = 0.046).

Quantum Yield Determination of β-Phenylcrotyl Chloride (12) in Acetone–Acetonitrile. β-Phenylcrotyl chloride (0.343 g, 2.06 mmol) was diluted to 10.0 ml in acetone–acetonitrile solution and 3.0 ml-aliquots were placed in two preconstricted Pyrex test tubes. The samples were then handled as outlined in method B. After 36 hr of irradiation and work-up as described before, one of the tubes contained 8.4% of **18** (ϕ = 0.046), while the other contained 7.1% of **18** (ϕ = 0.039).

Quenching of Rearrangement of β-Phenylcrotyl Chloride (12) by 1,3-Cyclohexadiene in Acetone–Acetonitrile. β-Phenylcrotyl chloride (0.217 g, 1.63 mmol) was diluted to 10.0 ml with acetone–acetonitrile solution, and 2.0-ml aliquots of this were placed in four preconstricted Pyrex test tubes. To these were added, respectively, 1.0-ml aliquots of 0.18, 0.09, 0.03, and 0.0 *M* solutions of 1,3-cyclohexadiene in acetone–acetonitrile. The tubes were handled as outlined in method B, and after 36 hr of irradiation and work-up as before, the following results were obtained: [diene] = 0.0 *M*, 8.2% of **18** (ϕ = 0.045); [diene] = 0.01 *M*, 6.9% of **18** (ϕ = 0.038); [diene] = 0.03 *M*, 1.8% of **18** (ϕ = 0.009); [diene] = 0.06 *M*, 0.9% of **18** (ϕ = 0.004).

Quantum Yield Determination of β-Chlorocrotyl Chloride (11) in Acetone–acetonitrile. β-Chlorocrotyl chloride (0.299 g, 2.39 mmol) was diluted to 10.0 ml with acetone–acetonitrile solution, and 3.0-ml aliquots of this were placed in two preconstricted Pyrex test tubes. The samples were then handled as described in method B. After 19 hr of irradiation and work-up as described before, one of the tubes contained 7.2% of **17** (ϕ = 0.076), while the other contained 6.5% of **17** (ϕ = 0.070).

Acknowledgment. This investigation was supported by Public Health Service Grant No. CA-13199 from the National Cancer Institute.

Registry No.—(*E*)-**9**, 53834-49-4; (*Z*)-**9**, 53834-50-7; (*E*)-**10**, 53834-51-8; (*Z*)-**10**, 53834-52-9; (*E*)-**11**, 15224-29-0; (*Z*)-**11**, 26310-41-8; (*E*)-**12**, 53783-48-5; (*Z*)-**12**, 53783-48-5; **13**, 55783-49-6; **14**, 2415-80-7; **15**, 53808-79-0; **17**, 7013-11-8; **18**, 53785-50-9; **19**, 1727-64-6; (*E*)-**21-Tl**, 53783-51-0; (*Z*)-**21-Tl**, 53783-52-1; (*E*)-**21-Me**, 53783-53-2; (*Z*)-**21-Me**, 53783-54-3; **22-Tl**, 55783-55-4; **22-Me**, 53783-56-5; (*E*)-β-phenylcinnamyl alcohol, 22835-64-9; (*E*)-β-chlorocinnamyl alcohol, 53783-57-6; (*E*)-β-chlorocrotyl alcohol, 53783-58-7; β-phenylcrotonaldehyde, 4411-89-6; (*E*)-β-phenylcrotyl alcohol, 53783-59-8; (*Z*)-β-phenylcrotyl alcohol, 53783-60-1; 1,3-cyclohexadiene, 592-57-4.

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Photocatalyzed Reaction of Trifluoromethyl Iodide with Steroidal Dienones[1]

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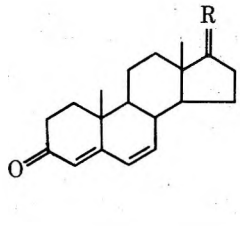
Received September 11, 1974

Ultraviolet irradiation (3500 Å) of pyridine solutions of 3-keto-$\Delta^{4,6}$-steroids in the presence of trifluoromethyl iodide gave 3-keto-4-trifluoromethyl-$\Delta^{4,6}$-steroids as the sole products of reaction. A similar reaction of using 7-oxo-3,5-androstadien-17β-yl acetate gave a mixture of 6-trifluoromethyl-7-oxo-$\Delta^{3,5}$-steroid and 3-trifluoromethyl-7-oxo-Δ^{5}-steroid indicating a steric as well as an electronic requirement for this reaction. An interesting reductive solvolysis of the 4-trifluoromethyl group has been observed.

In the course of preparing trifluoromethylated steroids,[2] we attempted photochemical addition of trifluoromethyl iodide to the 3-keto-$\Delta^{4,6}$ system. Haszeldine has shown the trifluoromethyl group adds selectively to the terminal vinyl carbon when acrylic acid derivatives are exposed to trifluoromethyl iodide under photolytic conditions.[3] The position of addition in these cases was not dependent upon polarization of the double bond but on the stability of the intermediate radical. Accordingly, Godfredsen and Vangedal demonstrated that addition to the steroidal 3-alkoxy-$\Delta^{3,5}$ system resulted in substitution at the 6 position.[4] Wolff found addition to Δ^{3}-5α-steroids gives exclusively the axial 3α-trifluoromethylated product,[5] a result expected if one invoked steric considerations. We find trifluoromethyl substitution occurs preferentially α to the carbonyl function in linearly conjugated dienone systems. Both electronic and steric considerations must then be involved in the addition of the trifluoromethyl radical to these electron-deficient systems.

Irradiation of a solution of dienones **1a–d** in a mixture of pyridine and trifluoromethyl iodide with uv light (3500 Å) for 2–6 days at room temperature gave 4-trifluoromethylated steroids **2a–d** as the only products (32–42% conversion) found in addition to starting material. That the trifluoromethyl group was in the 4 position was evidenced by PMR absorption of vicinal vinyl hydrogens at C-6 and C-7 (complex doublets at about τ 3.7 and 3.3, $J \simeq 11$ Hz). This absorption disappeared when **2a** and **2b** were hydrogenated in ethyl acetate in the presence of palladium–barium sulfate catalyst to give 3-keto-Δ^{4} derivatives **3a** and **3b**. It is interesting that compounds **2** and **3**, with maxima at 283 and 233 nm, respectively, show no bathochromic shift on substitution of a trifluoromethyl group for a hydrogen α to the carbonyl.

The "reversed" linear dienone **4** when irradiated in the presence of trifluoromethyl iodide led to two products in addition to recovered starting material. The major product isolated was 6-trifluoromethyl-3,5-dien-7-one (**5**) formed in



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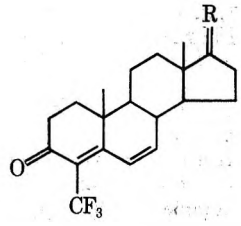

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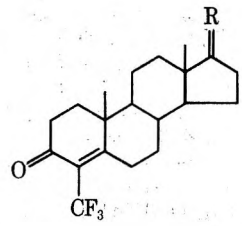

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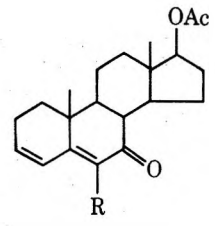
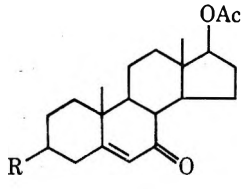
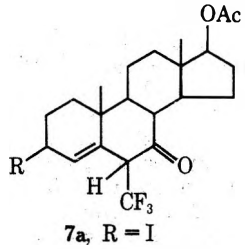


4, R = H
5, R = CF_3

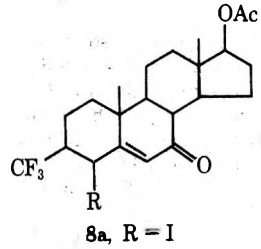
a, R = β-OAc, α-H
b, R = β-$COCH_3$, α-OAc
c, R = β-$OCH_2CH_2CH_2$-α
d, R = β-$CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$ α-H



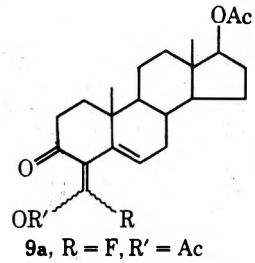
6a, R = CF_3
b, R = OAc



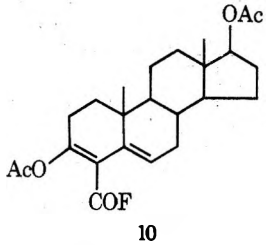
7a, R = I
b, R = radical



8a, R = I
b, R = radical



9a, R = F, R′ = Ac
b, R = OCH_3, R = Ac
c, R = H, R′ = H



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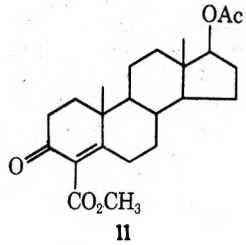

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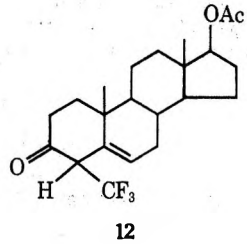
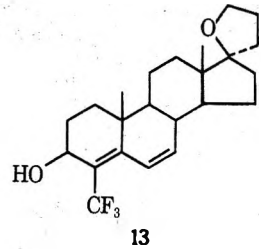


12



13

a manner similar to that described above. The second product had a molecular weight of 398 (mass spectrum), this being two units higher than for **5**. Ultraviolet (λ_{max} 237 nm), infrared (5.79 and 5.96 μm), and proton magnetic resonance (τ 4.26, vinyl hydrogen) spectra indicate the $\Delta^{5,7}$-one system remained intact. Comparison of the PMR spectrum of this material with 3β-acetoxy-7-oxo-Δ^5-steroid **6b** showed only slight differences in their respective 19-CH_3 and 6-H shifts. Structure **6a** is favored over the 4-substituted isomer whose PMR spectrum would be expected to show some change at one or both of those resonances. Configuration of the trifluoromethyl group remains unknown.

Interestingly, under these reaction conditions, addition α to the carbonyl affords dienone **5** whereas addition at the terminal δ position results in reduced product **6a**. It may be intermediate iodo compounds **7a** and **8a** are formed. Elimination would occur readily with **7a** due to the acidity of the proton α to the carbonyl group. The C-3 proton of **8a** is not as acidic and thus the allylic iodine atom could be removed reductively with hydrogen iodide generated within the reaction mixture.

If Haszeldine's conclusions are correct, these results imply the radical generated by attack α to the carbonyl (i.e., **7b**) is more stable than that generated by terminal attack on the dienone system (**8b**). Another factor is electron density in the dienone system is highest at the α position and the trifluoromethyl radical, being electrophilic, would be most disposed to attach to that point. Steric factors certainly must be considered, for δ addition occurred only when the α position was placed in a more hindered environment and the terminal end was more exposed as in **4**.

Hydrogenation of **2a** in methanol in the presence of a Pd/C catalyst resulted in the rapid uptake of greater than 1 equiv of hydrogen and formation of a mixture of products. When sodium acetate was added to moderate the rate and reaction was stopped after uptake of 1 equiv of hydrogen, a product containing an additional acetoxy group was formed. Depending on the manner of work-up, the major product (isolated yield, 24–50%) showed a molecular ion at either 418 or 430. Material of mol wt 418 had a proper elemental analysis for $C_{24}H_{31}FO_5$ and showed five absorption peaks in the range 5.50–6.14 μm of its infrared spectrum. These data would accommodate structures **9a** or **10**. Structure **9a** is favored as its uv maximum at 229 nm is near that of the similar cross-conjugated system **9c** (231 nm).[6] The compound of mol wt 430 is the corresponding methoxy steroid **9b**. This material when heated in wet methanol containing sodium acetate was transformed into 4-carbomethoxytestosterone acetate **11**.[7]

Lability of an olefinic trifluoromethyl group under such mild conditions is surprising. The trifluoromethyl groups of **2a** and **3a** were stable to refluxing methanolic sodium acetate indicating the catalyst and/or a reactive intermediate (i.e., **12**) play a part in formation of **9**.[8] Each trifluoromethyl dienone **2a** and **2b** when hydrogenated in ethyl acetate in the presence of fresh, but not pre-reduced palladium on barium sulfate catalyst gave an unidentified by-product in addition to a low yield of the dihydro product **3**. Reduction of **2c** with sodium borohydride in methanol gave alcohol **13** in good yield.

Experimental Section[9]

17β-Acetoxy-4-trifluoromethyl-4,6-androstadien-3-one (2a). A solution of 2.40 g of 17β-acetoxy-4,6-androstadien-3-one (**1a**) in a mixture of 10 ml of pyridine and 8 g of trifluoromethyl iodide was irradiated in a sealed Pyrex tube for 3.5 days at room

temperature. The tube containing the dark mixture was then cooled and opened. The mixture was acidified by addition to excess 2.5 *N* HCl. The product was extracted into chloroform and was washed successively with water, 5% aqueous $NaHSO_3$, and water. After drying ($CaSO_4$) and concentration, the residue (~3 g) was chromatographed on 150 g of silica gel. The trifluoromethyl compound **2a** (1.157 g) which eluted with benzene was recrystallized from heptane to give 0.990 g of heavy, pale yellow needles: mp 156–158°; $[\alpha]^{25}D$ +94.3°; uv max (CH_3OH) 283 nm (ϵ 2.3 × 10^4); ir 5.78, 5.97, 6.17, and 6.39 μm; PMR τ 3.29 (complex doublet, 1, J = 11 Hz, 7-CH), 3.69 (complex doublet, 1, J = 11 Hz, 6-CH), 7.96 (s, 3, CH_3CO), 8.87 (s, 3, 19-CH_3) and 9.10 (s, 3, 18-CH_3); *m/e* 396, 354, 336, 321, and 133.

Anal. Calcd for $C_{22}H_{27}F_3O_3$: C, 66.65; H, 6.87; F, 14.38. Found: C, 66.88; H, 6.70; F, 14.30.

Continued elution of the column afforded 0.330 g of material identified as the starting dienone **1a** by its infrared spectrum and thin layer chromatography behavior.

4-Trifluoromethyl-4,6-cholestadien-3-one (2d). A solution of 1.00 g of 4,6-cholestadien-3-one (**1d**) in 4 ml of pyridine and 3.4 g of trifluoromethyl iodide was irradiated as described above for 6 days. Workup and chromatography afforded 0.450 g of the trifluoromethylated steroid **2d.** Recrystallization of this material from hexane gave yellow prisms: mp 107–108°, $[\alpha]^{25}D$ +84.1°.

Anal. Calcd for $C_{28}H_{41}F_3O$: C, 74.63; H, 9.17; F, 12.65. Found: C, 74.38; H, 9.15; F, 13.06.

2′,3′α-Tetrahydrofuran-2′-spiro-17-(4-trifluoromethyl-4,6-androstadien-3-one) (2c). A solution of 1.00 g of the dienone **1c** in 6 ml of pyridine and 4.0 g of trifluoromethyl iodide was irradiated as described above for 2.5 days. Work-up and chromatography afforded 0.397 g of **2c.** Recrystallization from hexane gave 0.305 g, mp 122–125°. An analytical sample from methanol separated as pale yellow, heavy needles: mp 123–124°; $[\alpha]^{25}D$ +61.3°; uv max (CH_3OH) 285 nm (ϵ 2.4 × 10^4).

Anal. Calcd for $C_{23}H_{29}F_3O_2$: C, 70.03; H, 7.41; F, 14.45. Found: C, 69.91; H, 7.54; F, 14.67.

A solution of 30 mg of the above compound, **2c,** in 2.0 ml of methanol was treated at 0° with 10.0 mg of sodium borohydride with stirring. After 20 min, a drop of glacial acetic acid was added and the mixture was diluted with water. The product was worked up in ether solution to give 30 mg of a crystalline residue. Recrystallization from acetonitrile afforded 20.5 mg of the 3-ol **13** as small prisms: mp 194–195°; devoid of carbonyl absorption in its infrared spectrum; uv max (CH_3OH) 245 nm (ϵ 2 × 10^4); *m/e* 396 (M^+), 378, 319, 97.

Anal. Calcd for $C_{23}H_{31}F_3O_2$: C, 69.67; H, 7.88. Found: C, 69.25; H, 7.92.

17α-Acetoxy-4-trifluoromethyl-4,6-pregnadiene-3,20-dione (2b). A solution of 300 mg of the dienone **1b** in 2 ml of pyridine and 1.2 g of trifluoromethyl iodide was irradiated as described above for 4 days. Work-up and chromatography resulted in 149 mg of crystalline **2b** which separated from methanol as heavy prisms: mp 226–227°; $[\alpha]^{25}D$ +47.4°; uv max (CH_3OH) 283 nm (ϵ 2.4 × 10^4).

Anal. Calcd for $C_{24}H_{29}F_3O_4$: C, 65.75; H, 6.67; F, 13.00. Found: C, 65.50; H, 6.68; F, 12.81.

4-Trifluoromethyltestosterone Acetate (3a). A solution of 100 mg of the 4,6-dienone **2a** in 35 ml of ethyl acetate was hydrogenated at atmospheric pressure and room temperature in the presence of 60 mg of 5% palladium on barium sulfate catalyst. The reaction was stopped after theoretical uptake had occurred. The catalyst was separated and the solution concentrated to give 106 mg of a crystalline residue. Recrystallization from heptane gave 52 mg of fine needles, mp 130–144°. Concentration of the filtrate left crystalline material which when recrystallized twice from hexane amounted to 20 mg and had mp 138–144°. The infrared spectrum and thin layer mobility of this material was identical with that of the 130–144° melting material. It had uv max (isooctane) 233 nm (ϵ 1.3 × 10^4); PMR τ 5.36 (doublet of doublets, 1, 17-CH), 7.96 (s, 3, CH_3CO), 8.73 (s, 3, 19-CH_3), and 9.14 (s, 3, 18-CH_3).

Anal. Calcd for $C_{22}H_{29}F_3O_3$: C, 6.31; H, 7.33; F, 14.30. Found: C, 66.29; H, 7.55; F, 14.16.

A second material (mp 225–229°) isolated by thin layer chromatography (silica gel) of residues from work-up of the hydrogenation was analyzed by high resolution mass spectrometry and found to have an intense (molecular?) ion measured at 412.18409 mass units and corresponds best with an empirical formula of $C_{22}H_{27}F_3O_4$.

17α-Acetoxy-4-trifluoromethylprogesterone (3b). A solution of 438 mg of dienone **2b** in 35 ml of ethyl acetate was hydrogenated in the presence of 200 mg of 5% palladium on barium sulfate catalyst. The hydrogenation was stopped after uptake of 1 equiv. The catalyst was removed and the filtrate concentrated to a slowly crystallizing gum. Recrystallization in three steps using acetonitrile, benzene–hexane, and then methanol gave 47 mg of **3b,** mp 241–243°. The filtrates were combined and concentrated. The residue was eluted with 4:1 benzene–ethyl acetate on 78 g of Silica Gel H using the dry column technique. The eluent was collected in 5-ml fractions using a fraction collector. Additional **3b** (108 mg) was obtained in the early fractions. Recrystallization of this material gave 57 mg: mp 241–244°; uv max (MeOH) 241 nm (ϵ 1.1 × 10^4); PMR τ 7.91 (s, 3, CH_3CO_2), 7.99 (s, 3, 21-CH_3), 8.76 (s, 3, 19-CH_3), and 9.33 (s, 3, 18-CH_3); *m/e* 440 (M^+) 398, 397, 380, 355, and 337.

Anal. Calcd for $C_{24}H_{31}F_3O_4$: C, 65.44; H, 7.09; F, 12.94. Found: C, 65.51; H, 7.00; F, 12.83.

Continued elution gave 41 mg of starting dienone **1b** identified by its TLC mobility and infrared spectrum. Another crystalline component (121 mg) eluted next. This material was recrystallized from ether by addition of hexane to give prisms: mp 195–198°; uv max (CH_3OH) 236 nm (E% 220); ir 2.85 and 3.02 (OH), 5.80 (acetate), 5.90 (unsatd C=O?) and 6.26 μm (C=C); PMR τ 4.76 (narrow m, 1), 7.98 (s, 3, CH_3CO_2), 8.03 (s, 3, 21-CH_3), 8.60 (s, 3, 19-CH_3), and 9.35 (s, 3, 18-CH_3); *m/e* (no $M^{\cdot+}$), 455 (highest *m/e*), 410, 369, 353, 351, and 335.

Anal. Found: C, 61.15; H, 6.43; F, 12.43.

17α-Acetoxy-4-trifluoromethylprogesterone (3b). A suspension of 200 mg of 5% palladium on barium sulfate catalyst was prereduced in 10 ml of degassed ethyl acetate. A solution of 436 mg of the dienone **2b** in 25 ml of degassed ethyl acetae was added under hydrogen. Hydrogen uptae ceased after 30-min stirring at 25° and atmospheric pressure. The catalyst was removed and the filtrate concentrated to a crystalline residue. Recrystallization from ethanol gave 239 mg of **3b,** mp 236–240°, identical with the material described above in its spectral properties.

Photolysis of Trifluoromethyl Iodide in the Presence of 7-oxo-3,5-androstadien-17β-yl Acetate. A mixture of 0.800 g of the dienone **4** in 6.0 ml of pyridine and 6.2 g of trifluoromethyl iodide was irradiated as described above for 7 days. The material went into solution gradually and the mixture became dark. Workup in ethyl acetate resulted in ~1.0 g of dark residue. Vapor phase chromatography (VPC) indicated the mixture to contain three major components in the approximate ratio of 2:4:3 (order of elution). The last eluted major component corresponded to the starting dienone **4.** The residue was chromatographed on a column prepared from a mixture of 100 g of Stahl Silica Gel and 75 g of diatomaceous earth. Elution with benzene (4 l.) and then 2% ether in benzene (25-ml fractions using a fraction collector) gave after a small forerun 268 mg of crystalline **5.** After separation from heptane and then methanol, 135 mg was obtained, mp 148–152°. This material corresponded to the second eluted material by VPC. An analytical sample had mp 149–151°, $[\alpha]D$ −351°; uv max (CH_3OH) 278 nm (ϵ 1.98 × 10^4); PMR τ 3.28 (complex doublet, J = 11 Hz, 3-CH), 3.58 (complex doublet, J = 11 Hz, 4-CH), 7.96 (s, CH_3CO), 8.82 (s, 19-CH_3) and 9.15 (s, 18-CH_3), *m/e* 396 (M^+), 336, 320, 255 (base), 242, and 229.

Anal. Calcd for $C_{22}H_{27}F_3O_3$: C, 66.65; H, 6.87; , 14.38. Found: C, 66.24; H, 6.78; F, 14.74.

Continued elution (fractions 220–275) afforded 76 mg of crystalline material corresponding to the first VPC eluted major product. Recrystallization from heptane gave 27.5 mg of **6a,** mp 225–228° with crystal modification >200°; ir 5.80, 6.00, and 6.13 (shoulder) μm; uv max (CH_3OH) 236 nm (ϵ 1.28 × 10^4); PMR τ (HR-100) 4.25 (partially resolved doublet, width at half-height, 3.5 Hz), 7.98 (s, CH_3CO), 8.78 (s, 19-CH_3) and 9.19 (s, 18-CH_3); *m/e* 398 (M^+, base), 338, 323, 257, 244, and 231. The PMR (HR-100) of 3β-acetoxy-17-hydroxy-5-androsten-7-one had τ 4.28 ($w_{1/2}$ = 3.2 Hz) and 8.78 (s, 19-CH_3).

Anal. Calcd for $C_{22}H_{29}F_3O_3$: C, 66.31; H, 7.33. Found: C, 66.74; H, 7.13.

Continued elutions (fraction 315–350) afforded 151 mg of crystalline starting dienone, identified by its melting point and ir spectrum.

Hydrogenation of 2a in Methanolic Potassium Acetate. A solution of 100 mg of the trifluoromethyl dienone **2a** and 1.00 g of potassium acetate in 30 ml of methanol was hydrogenated at room temperature and atmospheric pressure in the presence of 25 mg of 10% palladium on charcoal catalyst. One equivalent of hydrogen (5.9 cm^3) was quickly absorbed and the reaction was stopped. The catalyst was removed and the filtrate was concentrated at room temperature to a small volume. After dilution with water, the product was separated by filtration, washed with water, and dried

under reduced pressure. Preparative thin layer chromatography of the residue (silica gel eluted with 4:1 benzene–ethyl acetate) resulted in the isolation of 25 mg of the major component. When quickly recrystallized from methanol, fine crystalline material was obtained, mp 180–193° slow decomposition, then rapid gas evolution: uv max 229 nm (ϵ 1.1 × 10^4) and shoulder 260 nm (ϵ 5 × 10^3); ir 5.51, 5.69, 5.81, 6.00, and 6.15 μm; PMR (T-60) τ 4.16 (narrow m, 6-CH), 7.93 (s, CH_3CO), 7.97 (s, CH_3CO), 9.18 (s, 19-CH_3), and 9.42 (s, 18-CH_3); *m/e* 418, 376, 356 (base), 328, 164, 162, and 133; metastable peaks at *m/e* 335 and 302 confirmed the fragmentation sequence, *m/e* 376 → 356 → 328.

Anal. Calcd for $C_{24}H_{31}O_5F$: C, 68.87; H, 7.47; F, 4.54. Found: C, 68.64; H, 7.72; F, 4.96.

In an attempt to repeat the above experiment with 0.5 g of **2a**, the same conditions were used except heat (bath temperature ~50°) was used when concentrating the filtrate after removal of the catalyst. In this case, the major product isolated, **9b** (250 mg, preparative TLC), was different from that described above in that it had mp 155–160°; *m/e* 430 (M^+), 388, 356 (base), 328, 164, 162, and 133; uv max 230 nm (ϵ 1.8 × 10^4); ir 5.62 and 5.73 μm; PMR (T-60) τ 4.55 (m, 6-CH), 6.29 (s, OCH_3), 7.90 (s, O_2CCH_3), 7.99 (s, O_2CCH_3), 8.99 (s, 19-CH_3) and 9.20 (s, 18-CH_3).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 68.95; H, 8.03.

A solution of 200 mg of this material (**9b**) in a mixture of 10 ml of methanol, five drops of water, and 200 mg of potassium acetate was heated at reflux for 16 hr under nitrogen. The mixture was concentrated and then the residue was extracted with ethyl acetate. After drying and concentration, the residue was eluted on a thick layer (1000 μ) silica gel-coated plate. The major component **11** was extracted and crystallized from methanol, 70 mg: mp 147–149°; *m/e* 388 (M^+), 356 (base), 332, and 328; uv max 244 (ϵ 1.08 × 10^4) and 287.5 nm (ϵ 1.72 × 10^3); ir 5.77, 5.97, and 6.19 μm; PMR τ 6.21 (s, OCH_3), 7.98 (s, O_2CCH_3), 8.77 (s, 19-CH_3), and 9.17 (s, 18-CH_3).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 68.56; H, 8.25. Found: C, 68.16; H, 8.27.

Stability of the Trifluoromethyl Steroids 2b and 3b to Methanolic Sodium Acetate. A solution of 20 mg of each of the steroids **2b** and **3b** was dissolved with 200 mg of sodium acetate in 5 ml of methanol. These solutions were heated at reflux for 30 min, then cooled and concentrated. The ethyl acetate extracts of the respective residues were concentrated to a crystalline material which, after recrystallization, were identified by mixture melting point, ir spectra, and TLC mobilities with their corresponding starting materials.

Acknowledgment. The authors wish to thank Dr. Byron Arison and Mr. Jack L. Smith for their assistance in interpreting the NMR and mass spectra discussed in this paper.

Registry No.—**1a**, 2352-19-4; **1b**, 425-51-4; **1c**, 6693-79-4; **1d**, 566-93-8; **2a**, 53821-28-6; **2b**, 53821-29-7; **2c**, 53821-30-0; **2d**, 53821-31-1; **3a**, 53821-32-2; **3b**, 53821-33-3; **4**, 13583-12-5; **5**, 53821-34-4; **6a**, 53821-35-5; **9a**, 53821-36-6; **9b**, 53821-37-7; **11**, 53821-38-8; **13**, 53835-06-6; trifluoromethyl iodide, 2314-97-8.

References and Notes

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(7) S. Julia and C. Huynh, *C. R. Acad. Sci., Ser. C*, **270**, 1517 (1970).
(8) Trifluoromethyl substituents become labile to nucleophiles when attached to (potentially) electron rich carbon atoms; see Y. Kobayashi, I. Kumadaki, Y. Hirose, and Y. Hanzawa, *J. Org. Chem.*, **39**, 1836 (1974); N. W. Gilman and L. H. Sternback, *J. Chem. Soc., Chem. Commun.*, 465 (1971).
(9) Melting points were determined on a Kofler hot-stage and are uncorrected. Infrared spectra were determined with a Perkin-Elmer spectrometer, Model 137, as chloroform solutions and are in accord with the assigned structures. PMR spectra were obtained from deuteriochloroform solutions with a Varian Model A-60A spectrometer unless otherwise noted. Mass spectra were obtained on either a CEC Model 21-110 or an LKB Type 9000 spectrometer by the direct probe technique. Rotational data were obtained from 1% chloroform solutions. Irradiations were carried out in a Rayonet photochemical reactor, Type RS, using lamps with peak intensity at 3500 Å. All isolated products were analyzed by thin-layer chromatography on silica gel-coated glass plates eluted with an appropriate benzene–ethyl acetate system.

Total Syntheses of Optically Active 19-Norsteroids. (+)-Estr-4-ene-3,17-dione and (+)-13β-Ethylgon-4-ene-3,17-dione

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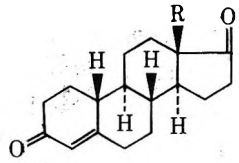
Received October 9, 1974

Highly efficient total syntheses of the title 19-norsteroids are described in which the chirality is introduced early in the synthetic scheme *via* an asymmetric synthesis of the bicyclic intermediates **4a** and **4b**. These substances are then converted in five stages into the key α-methylene ketones **9a** and **9b**. Michael addition of the β-keto ester **17** (prepared starting from diketene and formaldehyde) to the enones **9** followed by cyclization, saponification, and decarboxylation then affords the tricyclic compounds **20a** and **20b** which are readily transformed into the title diones in three additional stages. The efficiency of this approach is demonstrated by the production of **1a** and **1b** in overall yields of 27 and 18%, respectively, based on the starting 2-alkyl-1,3-cyclopentanediones.

In a previous publication,[2] two of us described a convergent, stereo-controlled total synthesis of racemic 19-norsteroids in which the synthetic strategy involved initial construction of a bicyclic C,D-ring synthon followed by elaboration of ring B and finally ring A. We now wish to present the results of a team effort directed toward the application of this scheme to the production of optically active 19-norsteroids of biological and commercial significance.[3] In particular, we wish to describe highly efficient and practical syntheses of diones (+)-**1a**[3,4] and (+)-**1b**[5] in which all carbon atoms of the final steroid molecule are derived from readily available building blocks. Furthermore, the crucial problem of introduction of chirality is solved *via*



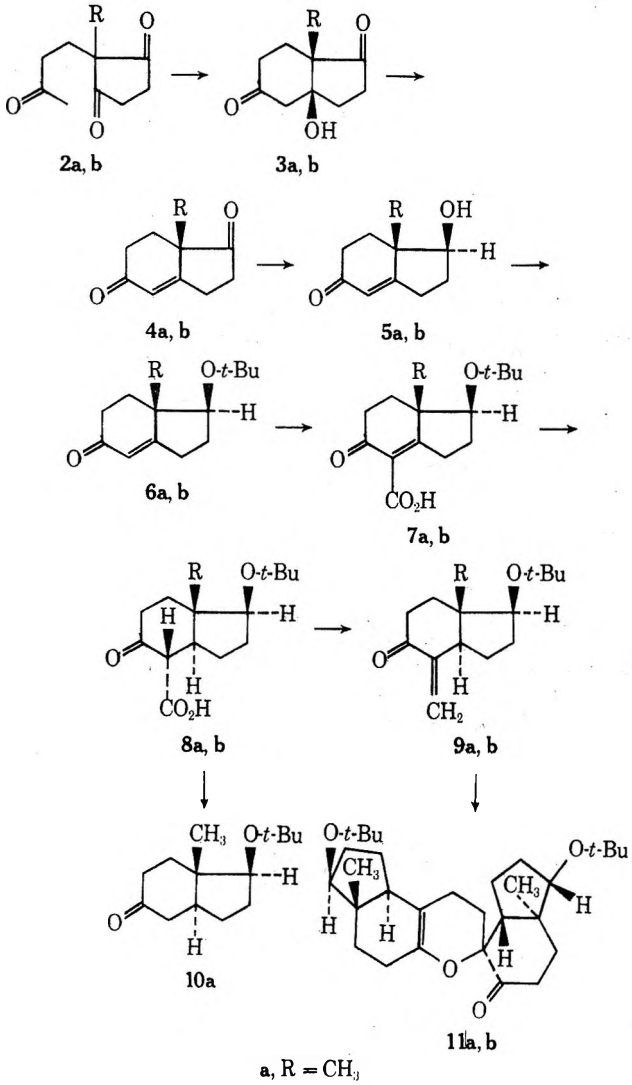
1a, R = CH_3
b, R = C_2H_5

an asymmetric synthesis[6] of the aforementioned C,D-bicyclic intermediates carried out at the earliest possible stage of the synthetic pathway. In order to avoid unnecessary repetition of the previously described work, we will not discuss each transformation in detail. Instead, we have chosen to concentrate on those areas in which substantial modifications of previous procedures were required and to emphasize pertinent experimental data which demonstrate the potential of this approach.

Results

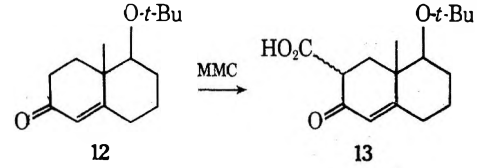
A. Synthesis of the α-Methylene Ketones 9a and 9b. The starting materials, triketones **2a** and **2b** (Scheme I), were prepared and cyclized with *S*-proline in *N,N*-dimethylformamide (DMF) on a 50–250-g scale, essentially as described previously.[6,7] In the angular methyl series, the crude ketol **3a** was directly dehydrated with *p*-toluenesulfonic acid giving enedione **4a** in 90–94% overall yield. This material was used as such without further purification. In the homologous series, the ketol **3b** was purified by recrystallization prior to dehydration which procedure allowed isolation of pure enedione **4b** in 65% yield. Selective reduction of these enediones with sodium borohydride[8] followed by treatment of the resulting ketols **5**[9] with isobutylene–phosphoric acid–boron trifluoride etherate[10,11] gave the keto ethers **6** in essentially quantitative yield.

Scheme I



The efficient preparation of the unsaturated keto acids **7a** and **7b** proved to be one of the major challenges encountered in this work. The original method involving carbonation of the sodio enolate of **6a** with CO_2[12] gave low direct yields (25–45%) of the desired acid **7a** thus requiring extensive recycling of the recovered enone. Subsequently, it was found that direct carbonation of **6a** with magnesium methyl carbonate (MMC) in DMF[13] afforded the desired keto acid **7a** in 64% yield, whereas similar carbonation of the homologous enone **6b** produced **7b** in 41% yield.[14] Pyrolysis of the mother liquor residues obtained after purification of the keto acids **7** caused decarboxylation of any regioisomeric 6-ξ-indancarboxylic acids present. Distillation then allowed recovery of the starting enones **6** which could be recycled (on a much smaller scale than required with the NaH–CO_2 procedure) thus raising the overall yields of the desired keto acids to 74% (**7a**) and 53% (**7b**).

The success of the MMC reaction is most likely due to the enhanced stability of the resultant magnesium chelates produced (relative to the analogous sodium derivatives formed using the NaH–CO_2 procedure) thus reducing the reversibility of the carbonation process. The regioselectivity observed in both carbonation procedures is apparently due to the preferance for heteroannular dienolate formation in indanones such as **6**. In this regard, it should be noted that the decalone derivative **12** afforded keto acid **13**



as the major carbonation product upon treatment with MMC under the conditions employed for the indanone cases. Similar results have been reported by Julia and Huynh.[15]

The high stereospecificity observed[12] in the hydrogenation of acid **7a** eliminated the need for a great deal of investigation at this stage. However, during the course of the hydrogenation and work-up, some decarboxylation of the unstable, saturated keto acids **8** was found to occur. In order to minimize this side reaction, the hydrogenations were carried out at 0° in methanol, a solvent which can then be readily removed also at low temperature (*ca.* 10°).

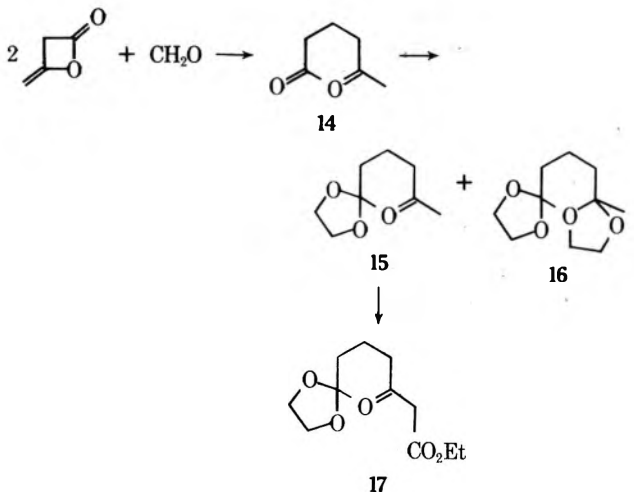
Two major side reactions were found to plague the decarboxylative Mannich reaction by which the keto acid **8a** is converted into the key α-methylene ketone **9a**,[2,16] namely decarboxylation of the starting material to the indanone **10a** and dimerization of the product giving rise to **11a**. Both of these side reactions were minimized by reducing the reaction time and by operating at low temperatures. The degree of dimerization was further controlled by simplifying the work-up procedure so that the product could be isolated more rapidly. From a study of the catalyst system, it was determined that the conversion of **8a** to **9a** was greatly accelerated by base catalysis which enabled large scale reactions to be completed in 1 day. For example, the following results were obtained upon reaction of **8a** in DMSO with formaldehyde: (a) no catalyst (24 hr, 20°), uv 60–65% **9a**; (b) 0.1–1.0 equiv of piperidine hydrochloride (3 hr, 20°),[2] 80–85% **9a**; (c) 0.1 equiv of piperidine or pyrrolidine (15 min, 20°), 95% **9a**. In the case of both **9a** and its homolog **9b**, the crude methylene ketone preparations were used without further purification.

The structure of the dimer **11a** rests mainly on spectral data and on analogy to the work of Eschenmoser and coworkers[17] in the onocerol series. Of the possible stereoiso-

mers, the endo-trans-trans, as indicated, seems most probable.

B. Synthesis of the Annulating Agent 17. The original procedure[2] for the preparation of the annulating agent, β-keto ester **17**, although attractive for small scale operation, was not readily adaptable to large scale preparations. Thus, a more practical synthesis of this substance was developed as shown in Scheme II. On warming an aqueous solution of

Scheme II

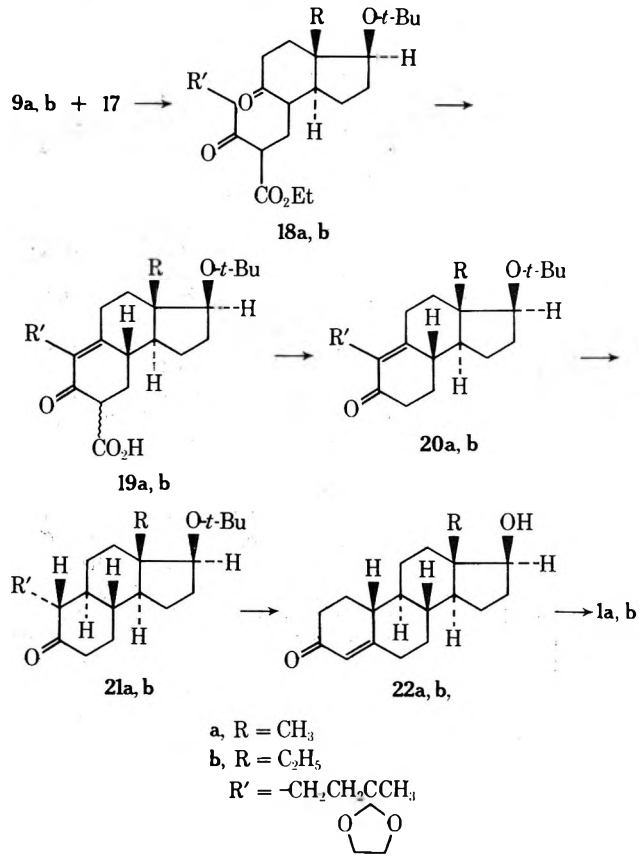


diketene (2 mol) and formaldehyde (1 mole) to 40°, copious amounts of CO_2 were evolved and 2,6-heptanedione (**14**)[18] could be isolated in 40% yield. We assumed that diketene was being hydrolyzed to acetoacetic acid which could then react *via* decarboxylative alkylation with formaldehyde to give 4-hydroxy-2-butanone. We further suspected that the latter material would suffer dehydration to yield methyl vinyl ketone. However, when acetoacetic acid was allowed to react with methyl vinyl ketone, only a 3.5% yield of **14** was obtained suggesting that methyl vinyl ketone is not, in fact, a preferred intermediate under our experimental conditions.

As anticipated, monoketalization of the symmetrical diketone **14** posed some problems. Under all conditions employed we obtained an equilibrium mixture of starting diketone, monoketal **15**,[2] and diketal **16**. However, by working in a two-phase system, with an excess of ethylene glycol at, 0°, we were able to direct the ketalization toward the formation of the desired monoketal as the major product. Separation of the reaction mixture efficiently into its three primary components was accomplished by means of a chemical separation since fractional distillation was unsuccessful in achieving this end. The monoketal and the small amount of unreacted diketone formed sodium bisulfite addition compounds from which the diketal could be separated by ether extraction. Selective liberation of the desired monoketal was achieved by careful pH control. The recovered diketal could be partially hydrolyzed to an equilibrium mixture resembling the original ketalization product and was therefore recycled into the sodium bisulfite separation of a subsequent batch. In this fashion a 64% yield of the monoketal **15** could be isolated. Carbethoxylation of **15** with sodium hydride and diethyl carbonate gave the β-keto ester **17** in 83% yield.

C. Synthesis of 19-Norsteroids. The series of reactions[2] consisting of a Michael condensation between the methylene ketones **9a** and **9b** and the annulating agent **17** (→**18**), *in situ* alkaline cyclization–saponification (**18** → **19**) to form the steroid B ring and finally decarboxylation proceeded smoothly affording **20a** and **20b** in high overall yields. The formation of by-products was found to be minimized when a solution of the methylene ketone was slowly added (*ca.* 3 hr) to the annulating agent in methanolic sodium methoxide. Inverse or rapid addition of the annulating agent are detrimental and the impurities formed under these conditions are to a great extent carried through the subsequent reactions and can interfere with the purification of the end product.

Scheme III



a, R = CH_3
b, R = C_2H_5
R′ = $-CH_2CH_2CCH_3$ (O,O)

Hydrogenation of the tricyclic enones **20** was carried out essentially as described previously[2] although the use of triethylamine was not essential for producing high yields of the desired trans-anti-trans compounds **21**. The crude hydrogenation products were then treated with hydrochloric acid under conditions which caused ketal hydrolysis, cyclodehydration, and *tert*-butyl ether cleavage and led to 19-nortestosterone (**22a**)[19] and its 18-methyl homolog **22b**[20] in excellent yields. Oxidation[21] then afforded the target diones **1** which were readily purified by recrystallization.

In summary, we have described a highly efficient and stereoselective route to optically and chemically pure 19-norsteroids which requires a minimum amount of intermediate purification (although the intermediates can, in most instances, be readily isolated if desired). Utilizing this synthetic sequence, the diones (+)-**1a** and (+)-**1b** can be produced in overall yields of 27 and 18%, respectively, based on starting 2-alkyl-1,3-cyclopentanedione. This represents an average yield per chemical reaction of 93.4% in the **a** series and 91.4% in series **b**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Thin-layer chromatography was

carried out for the **a** series on silica gel plates prepared as follows: H_2O (68 ml) was added to 35 g of Mallinckrodt silica gel (Silic AR^R TLC-7GF-5, pH7, gypsum fluorescence, 5% $CaSO_4$). The mixture was shaken well for 1 min, and then spread 250 μ thick on glass plates. These were air dried and then heated at 100° for 1 hr. E. Merck, Darmstadt, Silica Gel 60F-254 tlc plates were utilized for the **b** series. Both types of plates were developed by spraying with H_2SO_4–MeOH 1:1 (v/v) and heating. Tlc solvent system A, EtOAc–C_6H_6 4:1 (v/v); B, C_6H_6–EtOAc 1:1; C, C_6H_6–EtOAc 4:1; D, C_6H_6–EtOAc 8:2; E, CH_2Cl_2–EtOAc 8:1; F, CH_2Cl_2–EtOAc–HOAc 16:1.0:0.25; G, C_6H_6–EtOAc 95:5; H, C_6H_6–EtOAc 1:2; I, C_6H_6–EtOAc 9:1. Most reactions (except hydrogenations) were carried out under an atmosphere of nitrogen. Unless otherwise stated, organic extracts were washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. Rotary evaporators were used for solvent removal at the temperatures indicated, generally with a water pump (*ca.* 20 mm) or with the aid of a high vacuum pump (*ca.* 0.5 mm). Ultraviolet spectra were measured in 95% EtOH solution on a Cary Model 14M spectrophotometer. Unless otherwise noted, nmr spectra were measured on a Varian A-60 instrument in $CDCl_3$ solution. Chemical shifts are reported relative to TMS as an internal standard. Infrared spectra were recorded on Beckman IR-9 or Perkin-Elmer 621 spectrophotometers. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Low resolution mass spectra were obtained on CEC21-110 or JMS-01SG instruments. Solvent abbreviations: PE = petroleum ether (bp 30–60°), ligroin = petroleum ether (bp 60–70°).

(+)-(7a*S*)-7,7a-Dihydro-7a-methyl-1,5(6*H*)-indandione (4a). Trione **2a** (250 g, 1.375 mol) (prepared from 2-methyl-1,3-cyclopentanedione in 88% yield, on a 200-g scale, as deeribed previously[7]) was dissolved in 1.375 l. of DMF (H_2O 0.05%) and 2.5 g of finely ground *S*-proline was added. The mixture was stirred at 23–26° for 22.5 hr. The solvent was removed (60°, high vacuum) and 261 g of a dark green oil was obtained. Tlc analysis (system B) showed the ketol **3a** as the main spot. This material was dehydrated in 800 ml of C_6H_6 containing 7.5 g of *p*-toluenesulfonic acid monohydrate, at reflux. After *ca.* 1.5 hr, 25 ml of H_2O was collected in a Dean-Stark apparatus. The cooled solution was washed (saturated $NaHCO_3$, and saturated NaCl solutions), the aqueous phases were extracted with C_6H_6, and the combined organic layers were evaporated to give 235 g of a dark green-brown oil. Flash distillation through a 5-cm Vigreux column (107–123° (0.07–0.08 mm)) afforded 211.8 g (94%) of **4a**, as a light yellow oil which crystallized upon cooling at *ca.* +3°, $[\alpha]^{25}D$ +319.21° (*c* 0.5, C_6H_6) {lit.[6] $[\alpha]^{25}D$ +367° (*c* 1, C_6H_6)}. Such material was used without further purification.

(+)-(3a*S*,7a*S*)-7a-ethyl-3a,4,7,7a-tetrahydro-3a-hydroxy-1,5(6*H*)-indandione (3b). A solution of 58.88 g (0.3 mol) of trione **2b** (prepared in 90% yield from 2-ethyl-1,3-cyclopentanedione, as described previously[6]) in 300 ml of DMF was stirred with 10.34 g (0.09 mol) of *S*-(−)-proline at 23° for 20 hr. The residual proline was collected by filtration, washed with Et_2O, and air dried (8.14 g, 78.6%, recovered). The solvents were removed (35° bath, 0.45–0.5 mm), and the over-weight (77.24 g), viscous residue was taken up in 250 ml of EtOAc and filtered through 480 g of silica gel (E. Merck AG, 0.05–0.2 mm). The column was eluted with 4.5 l. of the same solvent. By evaporation of the eluate *in vacuo*, a tan paste was obtained which was dried (55° (0.05 mm) for 0.5 hr) giving 54.79 g (93.2%) of crude β-hydroxy ketone (**3b**): $[\alpha]^{25}D$ +28.65° (*c* 1.745, $CHCl_3$); Uv analysis indicated *ca* 5% enedione **4b** was present.

This crude material was crystallized from 3.5 l. of Et_2O (with Norit treatment) and concentrated to 1.4 l. from which 28.0 g of **3b** was obtained after cooling overnight at room temperature. Concentration to 200 ml and 50 ml successively produced crops of 9.48 g and 1.31 g for a total of 38.80 g (66%) of **3b**: mp range 113–114.5°; $[\alpha]^{25}D$ +18.90° to 19.90° (*c* 1.0, $CHCl_3$) [lit.[6] mp 112–112.5°; $[\alpha]^{25}D$ +19.0° (*c* 1.0, $CHCl_3$)]. Tlc analysis (system B) showed only a single component for each crop.

(+)-(7a*S*)-7,7a-Dihydro-7a-ethyl-1,5(6*H*)-indandione (4b). Dehydration of 30.01 g (0.153 mol) of the ketol **3b** in 225 ml of C_6H_6 with 0.431 g of *p*-toluenesulfonic acid at reflux was complete in 45 min (2.4 ml of H_2O was collected). Work-up as described above for **4a**, and removal of the solvent *in vacuo*, gave an oil that crystallized upon cooling. There was obtained 27.03 g (99.2%) of **4b** as a cream colored powder: mp 57.5–59°; $[\alpha]^{25}D$ +263.19° (*c* 1.035, C_6H_6); uv max 241 nm (ϵ 10,960); tlc (system B) showed one component {lit.[6] mp 59–60°; $[\alpha]^{25}D$ +262° (*c* 0.95, C_6H_6)}. This material was used without further purification.

(+)-(1*S*,7a*S*)-7a-Methyl-7,7a-dihydro-1-hydroxy-5(6*H*)-indanone (5a). To a chilled (−10°) solution of indandione **4a** {120 g, 0.732 mol; $[\alpha]^{25}D$ +354° (*c*, 0.5, C_6H_6)} in 600 ml of absolute EtOH was added 7.5 g (0.19 mol) of $NaBH_4$ in 720 ml of the same solvent. The rate of addition was adjusted so as to maintain the internal temperature between −5 and −10° (*ca.* 0.5 hr). The reaction mixture was allowed to warm to +5° over a 50-min interval, and then cooled again to −10° at which point the pH was adjusted to between 5 and 7 with 2 *N* HCl. The solvent was removed *in vacuo* (45°), the aqueous residue was worked up by extraction with EtOAc giving a semisolid product which was dried at 45° (high vacuum). This afforded 117 g (96%) of indanone **5a.** Such material was used without purification. A similar preparation had $[\alpha]^{25}D$ +90° (c 1.0, C_6H_6). Recrystallization of such material from ether–PE afforded indanone exhibiting $[\alpha]^{25}D$ +97.7° (c 1.0, C_6H_6) {lit.[9] $[\alpha]^{25}D$ +90.4° (c 1.0, C_6H_6)}.

(+)-(1*S*,7a*S*)-7a-Ethyl-7,7a-dihydro-1-hydroxy-5(6*H*)-indanone (5b). Treatment of 26.88 g (0.151 mol) of indandione **4b** with 1.615 g (0.045 mol) of $NaBH_4$, as described for the **a** series, gave the indanone **5b,** 26.98 g (99%), as an oil: $[\alpha]^{25}D$ +70.3° (c 1.28, C_6H_6). The analytical specimen was obained by preparative tlc (solvent system B): $[\alpha]^{25}D$ +71.59° (c 0.95, C_6H_6); uv max 240 nm (ϵ 11800); mass spectrum *m/e* 180 (M^+).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.11; H, 8.84.

(+)-(1*S*,7a*S*)-1-*tert*-Butoxy-7a-methyl-7,7a-dihydro-5(6*H*)-indanone (6a). A CH_2Cl_2 solution (795 ml) of indanone **5a** (79.4 g, 0.477 mol) was stirred and cooled to −75°. To this was added 8.3 ml of H_3PO_4 (prepared by dissolving 4.0 g of P_2O_5 in 11.0 ml of 85% H_3PO_4), 19.8 ml of 47% boron trifluoride etherate and 400 ml of liquid isobutylene. The mixture was stirred for 1.5 hr at −75° and then overnight at room temperature. The reaction mixture was then poured into 795 ml of 2 *N* NH_4OH solution and the product was extracted with CH_2Cl_2. Solvent removal (45°) gave 102.54 g (97%) of the *tert*-butyl ether **6a,** which was used without further purifcation (tlc analysis with solvent system C). A sample of **6a** crystallized from PE as white needles: mp 62–65°; $[\alpha]^{25}D$ +55° (*c* 1.0, $CHCl_3$); uv max 238 nm (ϵ 13800).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.80; H, 10.13.

(+)-(1*S*,7a*S*)-1-*tert*-Butoxy-7a-ethyl-7,7a-dihydro-5(6*H*)-indanone (6b). The indanone **5b** (26.64 g, 0.148 mol) was converted into the correspondng *tert*-butyl ether, as described for the preparation of **6a.** There was obtained 34.19 g (98.3%) of **6b,** as a dark yellow oil, suitable for further conversions without purification: uv max 243 nm (ϵ 11,230); $[\alpha]^{25}D$ +58.71° (c 1.62, $CHCl_3$). A sample from a separate preparation was purified by chromatography on silica gel followed by vacuum distillation [bp 95–99° (0.025 mm)]. The colorless oil so obtained (homogeneous by tlc, solvent system D) had the following properties: $[\alpha]^{25}D$ +56.17° (c 0.99, $CHCl_3$); uv max 242 nm (ϵ 11,280); mass spectrum *m/e* 236 (M^+).

(+)-(1*S*,7a*S*)-5,6,7,7a-Tetrahydro-1-*tert*-butoxy-7a-methyl-5-oxo-4-indancarboxylic Acid (7a). To 50.0 g (0.225 mol) of compound **6a** {$[\alpha]^{25}D$ +54.2° (c 1.0, $CHCl_3$)} was added 335 ml of magnesium methylcarbonate[13] (MMC) (3.5 equiv, 2.3 *M*) in DMF. The reaction vessel was placed in an oil bath (preheated to 125°), the mixture was stirred, and N_2 was bubbled through the solution. The internal temperature (115°) was maintained for 2 hr (reaction progress monitored by tlc analysis, solvent system E). The solution was chilled and poured into a mixture of ice and concentrated HCl. The aqueous phase (pH 3) was extracted with C_6H_6, and the organic phase was then extracted with 15% Na_2CO_3 solution. Acidification of the basic phase followed by extraction with C_6H_6 gave, after removal of the solvent *in vacuo* (45°), 57.9 g of yellow-brown solid. This material was purified with Et_2O–PE. There was obtained 38.41 g (64.3%) of **7a** as a yellow solid, mp 100–103°, and sintering: $[\alpha]^{25}D$ +35.2° (c 1.0, $CHCl_3$). A sample of the acid, obtained from a different experiment, crystallized from Et_2O–PE as yellow plates: mp 103–109°; $[\alpha]^{25}D$ +36.9° (c 1.0, $CHCl_3$); uv max 247 nm (ϵ 9670).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.40; H, 8.30.

The mother liquor residue (14 g) from the above purification was stirred and heated in a 160° oil bath for 30 min. The residual material was then distilled at 0.5 mm, through a 15 cm Claisen head with the heating bath at 165–195°. There was obtained 5.11 g (10.2%) of pure, recovered keto ether **6a** which could be recycled.

(+)-(1*S*,7a*S*)-5,6,7,7a-Tetrahydro-1-*tert*-butoxy-7a-ethyl-5-oxo-4-indancarboxylic Acid (7b). Following the procedure of the preceding experiment, 33.99 g (0.144 mol) of **6b** was treated with 214 ml (3.5 equiv, 2.18 *M*) of MMC in DMF. However, the

crude carboxylic acid was not extracted with Na_2CO_3 from the C_6H_6 phase as above. Rather, the solvent was removed and the resulting oil was dried to constant weight (0.2 mm, 23°) giving 39.31 g of a brownish-orange, partially crystalline mass. Trituration with pentane afforded 14.31 g (35.5%) of **7b** as a pale yellow solid: mp 86–86.5°; $[\alpha]^{25}D$ +24.35° (c 1.08, $CHCl_3$). A second crop was obtained from the mother liquors, by recrystallization from pentane, as a yellow solid (2.25 g, 5.6%): mp 82–83.5°, $[\alpha]^{25}D$ +30.33° (c 1.055, $CHCl_3$). This material contained a trace of starting compound **6b** (tlc analysis, solvent system D) but was satisfactory for further conversions. An analytical sample of **7b** was obtained by recrystallization from pentane with Norit treatment giving large colorless needles: mp 88.5–90°; $[\alpha]^{25}D$ +20.66° (c 0.93, $CHCl_3$); uv max 242 nm (ε 8,550).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.85; H, 8.75.

Decarboxylation of the mother liquor residues from the above trituration by heating in toluene at reflux, followed by distillation, allowed recovery of the starting enone **6b**. By this process the total yield of **7b** was raised to 53% based on recovered starting material.

***rac*-4,4a,5,6,7,8-Hexahydro-5β-*tert*-butoxy-4aβ-methylnaphthalen-2(3*H*)-one (12).** The preparation of **12** from the corresponding alcohol[22] was performed essentially as described for the *tert*-butyl ether **6a**. The enone **12**, analyzed and used as obtained, had the following properties: mp 63–68°; uv max 243 nm (ε 13950).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.16; H, 10.24.

***rac*-1,2,3,5,6,7,8,8a-Octahydro-8β-*tert*-butoxy-8aβ-methyl-3-oxo-2ξ-naphthoic Acid (13).** Reaction of 1.4 g (5.94 mmol) of **12** with MMC, as described for **7a**, afforded after one crystallization from Et_2O, 0.57 g of racemic 2ξ-naphthoic acid (**13**), mp 101.5–103° dec (tlc analysis with solvent system E). Further recrystallization gave the analytical sample as colorless crystals: mp 106–108° dec; uv max 242 nm (ε 13100).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.85; H, 8.61.

(+)-(1*S*,3a*S*,4*S*,7a*S*)-1-*tert*-Butoxy-7a-methyl-3a,4,5,6,7,7a-hexahydro-5-oxo-4-indancarboxylic Acid (8a). A solution of the unsaturated acid **7a** [100 g, 0.376 mol; $[\alpha]^{25}D$ +34.0° (c 1.0, $CHCl_3$)] in MeOH (800 ml) was added to 10 g of 10% Pd on $BaSO_4$. The mixture was chilled in an ice bath to *ca.* 0° and hydrogenated at essentially atmospheric pressure until uptake ceased (*ca.* 35 min). The solvent was removed *in vacuo* (high vacuum pump) in a 10° water bath, to give 111.65 g of crude, oily saturated acid suitable for subsequent conversions (tlc analysis with solvent system F). This substance is relatively unstable and should be treated accordingly. The analytical sample of **8a** was obtained from another experiment as a semisolid foam: $[\alpha]^{25}D$ +36.3° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.73; H, 9.17.

(+)-(1*S*,3a*S*,7a*S*)-1-*tert*-Butoxy-3a,4,7,7a-tetrahydro-7a-methyl-5(6*H*)-indanone (10a). A 1.3-g sample of saturated keto acid **8a** was heated *in vacuo* at 90° for 30 min (monitored by tlc, solvent system C or F) and yielded 1.1 g of the indanone. One crystallization from MeOH–H_2O gave 0.72 g of **10a**: mp 39.5–40.5°; $[\alpha]^{25}D$ +82.2° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.35; H, 11.14.

(+)-(1*S*,3a*S*,4*S*,7a*S*)-1-*tert*-Butoxy-7a-ethyl-3a,4,5,6,7,7a-hexahydro-5-oxo-4-indancarboxylic Acid (8b). Hydrogenation of 17.21 g (0.061 mol) of **7b** in 172 ml of MeOH with 1.72 g of 10% Pd on $BaSO_4$ catalyst was carried out at 23° (*ca.* 3.25 hr). Evaporation of the solvent *in vacuo* (23°, high vacuum) gave 19.05 g (over-weight) of a semisolid product (tlc solvent system D): $[\alpha]^{25}D$ +16.9° (c 1.0, $CHCl_3$). Such material was used preferably the same day, for conversion to the methylene ketone (below). A separate sample of **8b**, prepared for analysis by crystallization from 1:1 MeOH–H_2O followed by trituration with cold pentane, had: mp 76–78° dec; $[\alpha]^{25}D$ +13.10° (c 0.95, $CHCl_3$); mass spectrum *m/e* 282 (M^+).

(+)-(1*S*,3a*R*,7a*S*)-1-*tert*-Butoxy-7a-methyl-3a,6,7,7a-tetrahydro-4-methyleneindan-5(4*H*)-one (9a). To 111.65 g (assumed to be 0.376 mol) of crude saturated keto acid **8a** (described above) was added a solution consisting of 240 ml of DMSO, 186 ml of approximately 37% aqueous HCHO (*ca.* 5 equiv), and 3.74 ml of piperidine (*ca.* 0.1 equiv) (exothermic on mixing, precooled before addition to the keto acid). The reaction mixture was stirred for 25 min, and then poured into 600 ml of a mixture of ice water and saturated NaCl solution (1:1). The product was isolated by extraction with Et_2O, then the organic extracts were washed with 5% $NaHCO_3$ and afforded, after solvent removal (water pump, 25°), 93.96 g of crude, orange-red, oily methylene ketone (tlc analysis system F). A sample dried *in vacuo* at room temperature exhibited uv max 232 nm (ε 4260). A sample of **9a** from another batch crystallized from MeOH–H_2O giving white crystals: mp 56–60.5°; $[\alpha]^{25}D$ +35.6° (c 1.0, $CHCl_3$); uv max 232 nm (ε 4760); nmr δ 5.94 (m, 1, CH=), 5.00 ppm (m, 1, CH=); ir ($CHCl_3$) 1690 (C=O), 1625 cm^{-1} (C=C).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.23; H, 10.38.

(+)-(1*S*,3a*R*,7a*S*)-1-*tert*-Butoxy-7a-ethyl-3a,6,7,7a-tetrahydro-4-methyleneindan-5(4*H*)-one (9b). The crude, saturated keto acid **8b** (19.05 g; containing some solvent—assumed to be 0.061 mol), prepared above, was converted into the corresponding methylene ketone **9b**, as described for the preparation of **9a**. There was obtained 15.17 g of a yellow semisolid: $[\alpha]^{25}D$ +15.27° (c 1.92, $CHCl_3$); uv max 232 nm (ε 4000) (tlc analysis with solvent system G). This material was used without purification.

Another sample was prepared for analysis by first crystallization from MeOH–H_2O, followed by chromatography (silica gel 50:1, eluted with C_6H_6–EtOAc 97.5:2.5), and finally preparative tlc (solvent system G). Removal of the solvent left a colorless crystalline residue: mp 57–60.5°; uv max 232 nm (ε 4,800); $[\alpha]^{25}D$ +5.56° (c 1.11, $CHCl_3$); nmr δ 5.93 (m, 1, CH=), 4.97 ppm (m, 1, CH=).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.68; H, 10.59.

(−)-1′,3-Di-*tert*-Butoxy-1,2,3,3a,4,5,6′,7′,7′a,8,9,9bα-dodecahydro-3aβ,7′aα-dimethyl-5′*H*-spiro[cyclopenta[*f*][2*H*]benzopyran[2,4′(3′a*H*)]indan]-5′-one (11a). Dimer **11a** was isolated from crude semisolid methylene ketone **9a** by trituration with cold (−20°) MeOH. The white, insoluble material was removed by filtration and recrystallized from warm MeOH giving white needles: mp 148–154°; $[\alpha]^{25}D$ −10.3° (c 1.0, $CHCl_3$); ir ($CHCl_3$) 1720 (C=O), 1685 cm^{-1} (C=C-O); mass spectrum *m/e* 472 (M^+).

Anal. Calcd for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 76.42; H, 10.16.

2,6-Heptanedione (14). A mixture of 1 l. of H_2O, 204 g (2.5 mol) of 37% CH_2O solution, and 420 g (5.0 mol) of diketene was stirred and carefully warmed to 40° (CO_2 evolution!). The exothermic reaction was maintained at 40° for 24 hr (for the first 6–8 hr water cooling was necessary, then slight warming was required), cooled, and saturated with NaCl. The oil which precipitated was extracted with C_6H_6, which in turn was washed with $NaHCO_3$ solution. The residue (196.4 g), after removal of the solvent (40° bath), was distilled through a 10-cm Vigreux column. The main fraction [**14**: 129.5 g (40%); bp 83–99° (7–10 mm)] was a colorless oil which crystallized upon standing (mp 32–34°) (lit.[18] mp 34°) and was used without further purification. It may be crystallized from Et_2O–hexane.

6-(1,3-Dioxolan-2-yl)-2-heptanone (15).[2] A heterogeneous mixture of 2,6-heptanedione (**14**) (100 g, 0.795 mol), ethylene glycol (200 g, 3.25 mol), and toluene (500 ml) was stirred for 20 min in an ice bath. Concentrated H_2SO_4 (36 g, 20 ml, 0.367 mol) was added and vigorous stirring was maintained at ice bath temperature for 35 min. The colorless, lower ethylene glycol layer was separated and washed twice with toluene. To the original toluene layer was added *at once* a slurry of 100 g of $NaHCO_3$ in 50 ml of H_2O. This basic phase was used in turn to wash the two toluene extracts. The three toluene extracts were then washed, in turn, with two portions of saturated NaCl solution. The combined organic layers were evaporated (water pump) and *ca.* 145 g of a colorless oil was obtained. Gc analysis[23] showed a mixture of **14**:**15**:**16** = 11:61:28.

The crude oil in 250 ml of Et_2O was extracted four times with 200-ml portions of *cold* 20% (w/v) $NaHSO_3$ solution. The organic phase consisted of mainly (86%) diketal **16** (47.2 g), which could be recycled (see below).

Isolation of the desired monoketal (**15**) was carried out as follows. The $NaHSO_3$ layers were added slowly (*foaming!*) to a stirred slurry of 150 g of $NaHCO_3$ in 250 ml of toluene. The pH of the aqueous layer was adjusted to 7.5[24] (*glass electrode*) by the addition of *ca.* 20–50 g of $Na_2CO_3 \cdot H_2O$ and stirred for 30 min. Extraction of the H_2O layer with toluene, followed by removal of the solvent from the combined organic extracts (water pump vacuum, then 100° bath at 14 mm), gave 63.9 g (47%) of **15** as a colorless oil, used without further purification [bp of **15**: 112–116° (10 mm)]. This material was *ca.* 95% pure by gc analysis.[23]

The diketal **16** was recycled in the following manner. The 47.2 g of isolated diketal residue described above was dissolved in 100 ml

of toluene and 2.5 ml of 0.1 *N* HCl was added. After refluxing for 15 min and immediately cooling in an ice bath, 3 ml of saturated $NaHCO_3$ solution was added, followed by 25 ml of saturated NaCl. The organic phase was separated, and the solvent was removed. The residue (40.8 g), which contained *ca.* 50–55% monoketal (**15**) by gc analysis,[23] can be added to the next batch prior to the $NaHSO_3$ extraction.

7-(1,3-Dioxolan-2-yl)-3-oxooctanoic Acid Ethyl Ester (17).[2] To 97.0 g (2.26 mol) of NaH (56% dispersion in oil), which had been rinsed with hexane in the usual manner, was added 236 g (2.0 mol) of freshly distilled diethyl carbonate, followed by 250 ml of anhydrous Et_2O. The slurry was stirred and heated at gentle reflux, and 172 g (1 mol) of monoketal **15** was added slowly. A constant H_2 evolution was usually observed after *ca.* 25 g of **15** had been added. This induction period may take up to 90 min. Only after this point has been reached, is the remainder (*ca.* 150 ml) of **15** added over a period of 3–4 hr. After the addition was complete, the mixture was heated for another 90 min, and then stirred overnight at room temperature. The reaction mixture was chilled in an ice bath, 40 ml of EtOH in 400 ml of toluene was added (over 15 min), and stirring was continued for 45 min. Decantation into 170 ml of glacial HOAc and 500 g of ice, saturation of the aqueous phase with NaCl, and extraction with toluene (which was subsequently washed with $NaHCO_3$) gave 256.7 g of a yellow oily product *ca.* 77% pure.[25] The main fraction from distillation through a 10-cm Vigreux column [125–144° (0.2 mm)] weighed 202.6 g (83%), assayed 89% pure,[25] and was suitable for use in the annulation reactions.

(−)-3β-*tert*-Butoxy-3aβ-methyl-1,2,3,3a,4,5,8,9,9aβ,9bα-decahydro-6-{2-(2-methyl-1,3-dioxolan-2-yl)ethyl}-7*H*-benz[*e*]inden-7-one (20a). To a mixture of 125.0 g (10% excess; 81% pure[25]) of β-keto ester **17** in 750 ml of 0.1 *N* NaOMe in MeOH, was added dropwise, over 3 hr, a solution of 93.96 g (assumed to be 0.376 mol) of crude methylene ketone **9a** in 380 ml of MeOH (the α-methylene ketone solution was kept chilled during the addition to reduce dimer formation). The reaction mixture was allowed to remain overnight (*ca.* 16 hr) at room temperature then the intermediate diketo ester **18a** which had formed was saponified and cyclized by the addition of 180 ml of 5 *N* NaOH solution followed by stirring for 1 hr at room temperature. Most of the MeOH was then removed at 25° (water pump), H_2O was added, and the solution was extracted with C_6H_6. The aqueous phase was chilled and acidified to pH 3 (6 *N* HCl). The product was extracted with EtOAc, and the solvent was removed *in vacuo* (water pump, 55°). The crude product at this point is mainly a mixture of the acid **19a** and the corresponding decarboxylated product **20a** (tlc, solvent system C). Complete decarboxylation of the above mixture was brought about by heating the material *in vacuo* (high vacuum pump), in an 80° bath, to constant weight (*ca.* 3.0 hr) giving 146.88 g of an orange-red oil: uv max 250 nm (ε 12750). This material was used without purification in the following step.

The analytical sample of **20a** was prepared from a different batch by chromatography (silica gel), followed by crystallization from MeOH–H_2O giving colorless solid: mp 75–76.5°; $[\alpha]^{25}D$ −19.6° (*c* 0.5, $CHCl_3$); uv max 249 nm (ε 14800).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.60; H, 9.74.

(−)-3β-*tert*-Butoxy-3aβ-ethyl-1,2,3,3a,4,5,8,9,9aβ,9bα-decahydro-6-{2-(2-methyl-1,3-dioxolan-2-yl)ethyl}-7*H*-benz[*e*]inden-7-one (20b). The crude methylene ketone **9b** (15.16 g) was allowed to react with 20.2 g (0.067 mol) of annulating agent **17** exactly as described for the formation of **18a**, above. The resulting methanol solution of **18b** was treated with 29.1 ml of 5 *N* aqueous NaOH solution and stirred for 1.25 hr, then the MeOH was removed *in vacuo*, water was added, and neutral impurities were removed by ether extraction. After acidification (6 *N* HCl) of the aqueous alkaline solution and extraction (EtOAc), as for the **a** series, 27.2 g of a yellow, oily mixture of **19b** and **20b** was obtained: uv max 251 nm (ε 11,375).

A 22.0-g portion of this crude material in 200 ml of toluene was refluxed for 30 min (tlc analysis with solvent system D). Removal of the solvent and trituration with ligroin gave 19.08 g of a semisolid. Partial purification of a 9.23-g portion was realized by removal of low boilers by distillation [130° bath (0.1 mm)]. The solid residue (7.46 g; mp 109.5–115°; $[\alpha]^{25}D$ −23.83° (*c* 1.15, $CHCl_3$); uv max 250 nm (ε 13,850); (*ca.* 91% pure) was used for the subsequent conversion. A similar preparation was filtered over silica gel (in Et_2O), crystallized from PE (with Norit treatment), and afforded the analytical sample of **20b** as colorless needles: mp 121.5–122°; $[\alpha]^{25}D$ −35.27° (*c* 1.16, $CHCl_3$); uv max 249 nm (ε 15,200).

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.22; H, 9.97. Found: C, 74.29; H, 9.85.

(+)-17β-Hydroxyestr-4-en-3-one (19-Nortestosterone) (22a). Crude **20a** (146.8 g, 0.376 mol) in 1.47 l. of 95% EtOH was added to 14.7 g of 5% palladium on carbon (Engelhard Industries) and hydrogenated at essentially atmospheric pressure at 65°. To the resulting ethanolic solution of **21a** (after filtration to remove the catalyst) was added 345 ml of 6 *N* HCl. The mixture was refluxed for 2.5 hr (monitored by tlc analysis, solvent system H). The solution was chilled and adjusted to pH 5, most of the EtOH was removed, and the aqueous residue was extracted with C_6H_6. The crude product (106.1 g) was obtained as a greenish-yellow oil. A sample, dried *in vacuo* (90°), exhibited $[\alpha]^{25}D$ +41.6° (*c* 1.0, $CHCl_3$); uv max 240 nm (ε 14400).

From an earlier run, a pure sample of **22a** was obtained by filtration over silica gel (in $CHCl_3$), followed by recrystallization (CH_2Cl_2–Et_2O): mp and mmp (with authentic **22a**) 117–118°; $[\alpha]^{25}D$ +58.7° (*c* 1.0, $CHCl_3$); uv max 240 nm (ε 16850). This preparation was identical by spectral and tlc comparison with authentic material (from Searle Chemicals, Inc.).

(+)-13β-Ethyl-17β-hydroxygon-4-en-3-one (22b). Compound **20b** (3.63 g, 8 mmol, *ca.* 91% purity by uv analysis) in 181.5 ml of a 0.5% solution of triethylamine in absolute EtOH was hydrogenated, as above, with 1.09 g of 5% palladium on carbon. The solvent was removed, and the crude oily product (4.07 g) which still contained some solvent was used directly.

The analytical sample of **21b** was obtained by hydrogenation of a pure sample of **20b**, as above. The crude product was recrystallized from pentane, and then from PE (−20°). Chromatography on silica gel (C_6H_6–EtOAc 75:25) and finally treatment with PE gave pure **21b:** mp 81.5–83°; $[\alpha]^{25}D$ −1.97°, $[\alpha]^{25}_{365}$ −133.77° (*c* 1.01, $CHCl_3$).

Anal. Calcd for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.54; H, 10.49.

The crude **21b** above (4.07 g) was dissolved in 43.5 ml of MeOH and 43.5 ml of 2 *N* HCl and heated at reflux for 4 hr (monitored by tlc, solvent system B). Work-up as for **22a** and trituration of the crude product with PE afforded 2.36 g of **22b,** as a crystalline solid: mp 146–151°; $[\alpha]^{25}D$ +40.73° (*c* 1.10, $CHCl_3$); uv max 240 nm (ε 15,900). This material was used directly.

A pure sample of **22b** was obtained from another experiment (as above). Crude cyclized product was triturated (PE), crystallized (EtOAc), and chromatographed on silica gel (30:1, C_6H_6–EtOAc). A final recrystallization from Et_2O gave **22b** as needles: mp 159–160°; $[\alpha]^{25}D$ +51.09° (*c* 1.01, $CHCl_3$); uv max 241 nm (ε 17,200) {lit.[20] mp 154–157°; $[\alpha]^{25}D$ +52.4° ($CHCl_3$)}.

(+)-Estr-4-ene-3,17-dione {(+)-19-Norandrost-4-ene-3,17-dione} (1a). A solution of 106.1 g of crude 19-nortestosterone (**22a**), described above, in 720 ml of acetone, was chilled to −5°. Jones reagent[21] (80 ml, 2.7 *M*) was added dropwise so that the temperature remained between −5 and 0° (*ca.* 1 hr) (monitored by tlc–solvent system H). Most of the acetone was then removed *in vacuo* (50°). The dark-green residue was diluted with ice water and extracted with C_6H_6. Removal of the solvent gave 92.76 g of crude dione. A small sample dried at 90° (0.005 mm) had the following properties: $[\alpha]^{25}D$ +114° (*c* 1.0, $CHCl_3$); uv max 240 nm (ε 14230). Recrystallization from CH_2Cl_2–Et_2O afforded 49.58 g of white, crystalline **1a:** mp 163–169.5°; $[\alpha]^{25}D$ +140° (*c* 1.0, $CHCl_3$). A second crop (1.43 g) was obtained: mp 155–163°; $[\alpha]^{25}D$ +134° (*c* 1.0, $CHCl_3$). Both crops were blended to afford the final product. Yield: 51.01 g (50%, based on the 100 g batch of crystalline acid **7a** used above); mp 163–169.5° (167.4–169.9° corrected); $[\alpha]^{25}D$ +139.4° (*c* 1.184, $CHCl_3$); uv max 238 nm (ε 16600) {lit.[4] mp 170–171°, $[\alpha]^{25}D$ +147°}.

(+)-13β-Ethylgon-4-ene-3,17-dione (1b). Oxidation (as described in the preceding experiment) of the 2.3 g of **22b** (described above) in 70 ml of acetone, with 2.8 ml of Jones reagent[21] (monitored by tlc–solvent system B), produced 2.2 g of crude dione **1b:** mp 148–166°; $[\alpha]^{25}D$ +81.4° (*c* 1.20, $CHCl_3$); uv max 240 nm (ε 16000). Recrystallization from acetone gave 1.0 g of colorless prisms, mp 174.5–175.5°, $[\alpha]^{25}D$ +97.80° (*c* 1.23, $CHCl_3$); uv max 239 nm (ε 17200). A second crop (0.415 g) was obtained, mp 172–174°, $[\alpha]^{25}D$ +97.77° (*c* 1.165, $CHCl_3$) {lit.[5] mp 175–176°; $[\alpha]^{23}D$ +92.9° (c 1.0, $CHCl_3$)}.

Acknowledgment. We wish to acknowledge many helpful discussions, related to this work, with Professors G. Büchi and W. G. Dauben. We are also indebted to Dr. A. Brossi for his advice and encouragement and to Dr. A. I.

Rachlin for guidance and assistance. Particular thanks go to Mr. L. A. Dolan and members of the Kilo Laboratory, Hoffmann-La Roche Inc., Nutley, N.J., for the preparation of large quantities of intermediates, which helped to expedite this project. We are also obligated to the personnel of the Physical Chemisty Department, Hoffmann-La Roche Inc., Nutley, N.J., under the direction of Dr. P. Bommer, for carrying out many of the spectral, microanalytical, and polarimetric determinations required in this work. Finally, we wish to express our appreciation for the valuable technical assistance provided by Mr. F. Bizzarro and Mr. R. Vass.

Registry No.—**1a,** 734-32-7; **1b,** 21800-83-9; **2a,** 25112-78-1; **2b,** 34927-33-8; **3b,** 35544-89-9; **4a,** 17553-86-5; **4b,** 33878-95-4; **5a,** 16271-49-1; **5b,** 53016-43-6; **6a,** 41878-38-0; **6b,** 53078-16-3; **7a,** 31944-51-1; **7b,** 53702-05-9; **8a,** 53702-06-0; **8b,** 53662-91-2; **9a,** 53702-07-1; **9b,** 53052-91-8; **10a,** 53662-92-3; **11a,** 53662-93-4; **12,** 53662-94-5; **12** corresponding alcohol, 50302-16-4; **13,** 53662-95-6; **14,** 13505-34-5; **15,** 15580-05-9; **17,** 27428-41-7; **20a,** 24157-07-1; **20b,** 53662-96-7; **21b,** 53662-97-8; **22a,** 434-22-0; **22b,** 793-55-5; diketene, 674-82-8; formaldehyde, 50-00-0.

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(24) If the pH is greater than 7.5, dione **14** starts to be liberated.
(25) Assayed by uv analysis: analytically pure **17** shows uv max (0.1 *N* $NaOCH_3$) 273 nm (ε 12500).

Novel Total Syntheses of (+)-Estrone 3-Methyl Ether, (+)-13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one, and (+)-Equilenin 3-Methyl Ether

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Received May 16, 1974

Conjugate addition of *m*-methoxybenzylmagnesium chloride to the optically active enones **1a** and **1b** in the presence of cuprous salts gives the key tricyclic ketones **2a** and **2b,** respectively, in good yields. Cyclization of the latter materials produces the 9,11-dehydro compounds **4a** and **4b** which can be converted into the target steroids **7a** and **7b** efficiently *via* the intermediates **5a,b** and **6a,b.** Treatment of **4a** with trifluoroacetic acid leads to disproportionation as well as *tert*-butyl ether cleavage and the formation of estrapentaene **8a** oxidation of which yields (+)-equilenin 3-methyl ether (**10a**). In contrast, exposure of **4a** to *p*-toluenesulfonic acid gives the mixture of estratetraenols **11a** and **12a.**

The homologous, optically active α-methylene ketones **1a** and **1b** are readily available intermediates of great utility in the total synthesis of 19-norsteroids[1] and androstanes.[2] In the previous work,[1,2] β-keto ester intermediates containing the carbon atoms destined to become rings A and B of the steroid nucleus were added in a Michael reaction to the enones **1.** It occurred to us that these unsaturated ketones should also be valuable for the production of estrone and related compounds[3] *via* a short and potentially efficient scheme involving, as the key transformation, conjugate addition of *m*-methoxybenzyl Grignard reagents or derived organocopper species[4] to the enone system producing the tricyclic ketones **2.** We have investigated this approach and report the results herein.

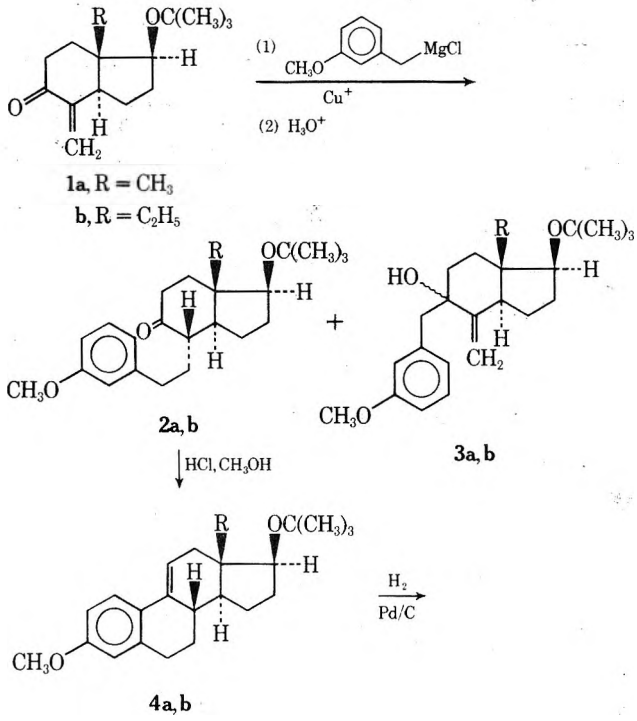
Results

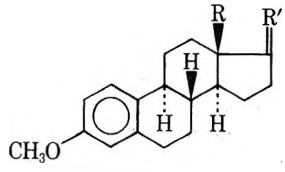
The reaction of *m*-methoxybenzylmagnesium chloride with enone 1a was found to be regioselective, in the desired mode, when carried out in the presence of cuprous ion. Under these conditions, it was possible to obtain the 1,4 adduct **2a** in 80–90% yield after chromatographic purification, the 1,2 adduct **3a** being formed in only minor amounts. In

contrast, when this reaction was carried out in the absence of cuprous ion, only the 1,2 adduct was obtained.[5] Repetition of the copper-catalyzed procedure using the homologous enone **1b** yielded the adduct **2b** in over 60% yield.

The adducts **2a** and **2b** obtained were preponderantly the stable epimers shown having the equatorial arylethyl 4 substituent. In one experiment, a small amount of the 4-axial epimer of **2b** was isolated during chromatographic purification. Treatment of this material with methanolic sodium hydroxide readily and quantitatively converted it into the stable epimer.

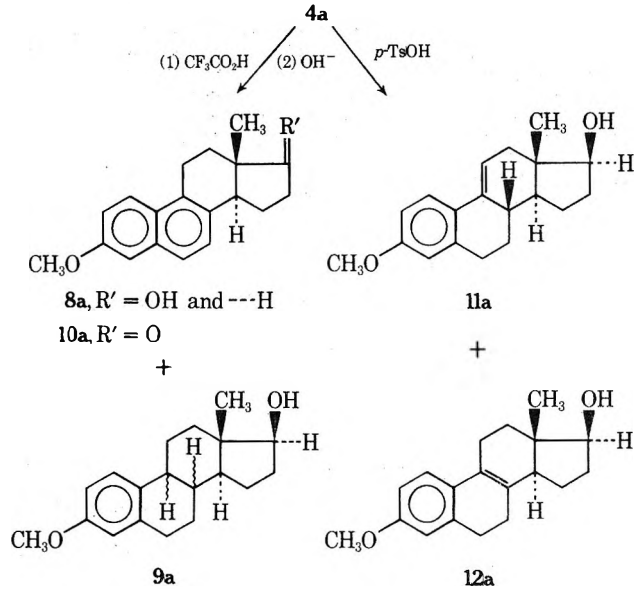
Cyclization of the tricyclic ketones **2a** and **2b** was effected at room temperature with methanolic hydrochloric acid[8] giving the crystalline tetraenes **4a** and **4b** in 77 and 85% yields, respectively. Under these conditions, essentially no cleavage of the *tert*-butyl ether moiety was observed.[9] Isolation of the intermediates **2** was unnecessary. Thus, for example, the crude product from addition of *m*-methoxybenzylmagnesium chloride to enone **1a** as described above could be directly cyclized affording pure **4a** in 71% overall yield.





Catalytic hydrogenation of **4a** over palladium on carbon was stereoselective and produced mainly the estratriene **5a** (54%[10]). Cleavage of the *tert*-butyl protecting group by treatment of **5a** with trifluoroacetic acid[9] then afforded estradiol 3-methyl ether (**6a**) which was directly oxidized[11] to estrone 3-methyl ether (**7a**). Repetition of this sequence without purification of **5a** allowed isolation of **7a** in 62% overall yield. In a similar manner, hydrogenation of **4b** gave the gonatriene **5b** (67%[10]) which was treated with *p*-toluenesulfonic acid[9] producing **6b**.[12,13] Oxidation of the latter material then yielded (+)-13β-ethyl-3-methoxygona-1,3,5(10)-trien-17-one (**7b**).[13,14] Since the chirality present in the starting enones **1** is introduced *via* a highly efficient asymmetric synthesis,[3f,15] the above scheme provides a direct route to optically active estranes and gonanes without the requirement of and disadvantages associated with classical resolutions[3c,12] or microbiological transformations.[13,14]

When cleavage of the *tert*-butyl ether in **4a** was carried out in trifluoroacetic acid at 0°,[9] disproportionation of the styrene system occurred concomitantly leading, after alkaline hydrolysis, to a product containing approximately equal parts (gc, uv analysis) of the estrapentaene **8a**[16] and a mixture of estratriene isomers **9a**.[17] Although separation of this mixture was preparatively difficult, column chromatography afforded a pure sample of **8a** which was shown to be identical with material produced from *d*-equilenin.[16] Oxidation[11] of the crude mixture of **8a** and **9a** gave *d*-(+)-equilenin 3-methyl ether (**10a**)[19,20] in low yield after purification using a combination of preparative thin layer chromatography and recrystallization. In contrast to the behavior of **4a** in trifluoroacetic acid, treatment of this substance with *p*-toluenesulfonic acid in refluxing benzene[9] allowed *tert*-butyl ether cleavage with essentially no disproportionation and produced a mixture consisting mainly of the estratetraenols **11a**[21] (major) and **12a**[12] (minor).



Experimental Section

Unless otherwise noted, work-up procedures involve three extractions with the specified solvent. Organic solutions were then combined, washed with brine, dried over anhydrous sodium or magnesium sulfate, filtered, and concentrated under water aspirator pressure at 40–50° on a rotary evaporator. The crude products were then dried under high vacuum to constant weight. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All reactions except hydrogenations were carried out under an inert atmosphere of either argon or nitrogen. Column chromatography was performed using Merck (Darmstadt) silica gel, 0.063–0.2 mm. Thin layer chromatography was carried out using Merck (Darmstadt) silica gel 60 F-254 plates. Plates were developed with the following solvent systems: (a) 1:1 hexane–ether; (b) 19:1 hexane–ether; (c) 19:1 benzene–ethyl acetate; (d) 1:1 benzene–ethyl acetate. Spots were detected with uv light and phosphomolybdic acid spray followed by heating. Tetrahydrofuran (THF) was dried over molecular seives and slurried over Woelm grade I neutral alumina just prior to use. A 5% palladium on carbon catalyst prepared at F. Hoffmann-La Roche and Co., AG, Basle, Switzerland and designated AK-4 was employed for the hydrogenations. Varian A-60 and HA-100 or Jeolco C-60H spectrometers were used to obtain the pmr spectra ($CDCl_3$ solution). Chemical shifts are reported relative to TMS. Infrared spectra ($CHCl_3$

solution) were recorded on Beckman IR-9 or Perkin-Elmer 621 spectrophotometers. The uv spectra (95% ethanol solution) were recorded on a Cary model 14M spectrophotometer. Low-resolution mass spectra were obtained on CEC 21-110 or JMS-01SG instruments. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter and, unless otherwise noted, in 1% chloroform solutions. Gas chromatographic analyses were carried out on samples trimethylsilylated with Regisil (Regis Chem. Co.-BSTFA containing 1% TMCS) using a Becker 409 instrument. A 3 ft × 0.25 in. column of 10% OV 101 on GC-Q 100–120, at 250°, with a nitrogen carrier gas flow of 30 ml/min was employed.

(1*S*, 3a*R*, 4*S*, 7a*S*)-(+)-1-*tert*-Butoxy-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-3a,4,7,7a-tetrahydro-5(6*H*)-indanone (2a). A solution of 19.5 g (0.125 mol) of *m*-methoxybenzyl chloride[22] dissolved in 118 ml of anhydrous THF was added dropwise over 45 min to a stirred suspension of 6.25 g (0.25 mol) of magnesium turnings in 25 ml of anhydrous THF at reflux temperature. The mixture was then stirred for an additional 30 min under reflux. After cooling to room temperature, 250 ml of anhydrous THF and 11.9 g (0.062 mol) of cuprous iodide were added and the mixture was stirred for 5 min, then cooled to −20° and stirred at this temperature for 5 hr. A solution of 4.5 g (0.019 mol) of methylene ketone **1a**[1a] in 50 ml of anhydrous THF was then added with stirring at −15° over a 30-min period. When the addition was complete, the resulting suspension was poured into a stirred mixture of ice and saturated NH_4Cl. After stirring for 20 min, the solids were filtered and washed with ether. The filtrate was worked up with ether in the usual manner gaving 19.97 g of viscous, oily product. This material was chromatographed on 200 parts of silica gel. Elution with 50:1 benzene–ethyl acetate gave first bis(*m*-methoxybibenzyl) and then 6.025 g (88%) of the keto ether **2a** as a viscous oil [tlc: R_f 0.5 (system c); 0.1 (system b)].

In another run, an analytical sample of **2a** was obtained by preparative thin layer chromatography (system c) followed by evaporative distillation giving a pale-yellow oil: bp 190–200° (bath) (0.01 mm); $[\alpha]^{25}D$ +27.46°; uv max 216 nm (ε 8200), 271 (2075), 278 (1875); ir 1705 (C=O), 1610, 1595 (anisole), 1390, 1365 cm^{-1} (*t*-C_4H_9); nmr δ 7.16 (m, 1, aromatic), 6.72 (m, 3, aromatic), 3.75 (s, 3, CH_3O), 3.45 (m, 1, C_1–H), 1.12 (s, 9, O-*t*-C_4H_9), 1.00 ppm (s, 3, C_{7a}–CH_3); mass spectrum *m/e* 358 (M^+).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.73; H, 9.73.

The 1,2 adduct **3a** [tlc: R_f 0.28 (system c)] was isolated as a viscous oil, by column chromatography, from fractions eluted after those containing **2a** and showed the following spectral properties: uv max 220 nm (ε 13010), 272 (2110), 280 (2020); ir 3600 (OH), 1650 (C=CH_2), 1395, 1365 cm^{-1} (*t*-C_4H_9); nmr δ 7.16 (m, 1, aromatic), 6.72 (m, 3, aromatic), 4.85 (m, 1, HC=), 4.60 (m, 1, HC=), 3.75 (s, 3, CH_3O), 3.62 (m, 1, C_1–H), 2.90 (m, 2, $ArCH_2$), 1.15 (s, 9, O-*t*-C_4H_9), 0.67 ppm (s, 3, C_{7a}–CH_3); mass spectrum *m/e* 358 (M^+). This material was the sole product when no cuprous salt was employed.

(+)-17β-*tert*-Butoxy-3-methoxyestra-1,3,5(10),9(11)-tetraene (4a). A. From 2a. A solution of 1.21 g (3.34 mmol) of keto ether **2a** in 100 ml of methanol was stirred at room temperature while 20 ml of 10 *N* aqueous HCl[8] was added dropwise over a 15-min period. The addition caused a mild exotherm and a precipitate appeared toward the end of the addition period. The resulting slurry was stirred at room temperature for 5.5 hr then kept at 0° for 16 hr. The colorless solid was filtered with suction and washed with water then dried under high vacuum giving 0.876 g (77.2%) of **4a**, mp 129–131°. Tlc analysis (system b) showed a single spot, R_f 0.35. Recrystallization of a sample prepared in this way from methanol gave colorless needles: mp 133–134°; $[\alpha]^{25}D$ +101.27°; uv max 264 nm (ε 19700), infl 290–300 (ε 3550); ir 1630 (C=C), 1610, 1580 (anisole), 1393, 1365 cm^{-1} (*t*-C_4H_9); nmr δ 7.48 (d, 1, *J* = 8 Hz, C_1–H), 6.58 (m, 2, C_2–H, C_4–H), 6.07 (m, 1, C_{11}–H), 3.74 (s, 3, OCH_3), 3.52 (m, 1, C_{17}–H), 2.78 (m, 2, C_6–H), 1.15 (s, 9, O-*t*-C_4H_9), 0.77 ppm (s, 3, C_{13}–CH_3); mass spectrum *m/e* 340 (M^+). A portion of this material was sublimed prior to combustion analysis at 115–120° (0.02 mm) giving colorless solid, mp 132–133°.

Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.01; H, 9.38.

B. From 1a Without Isolation of 2a. A solution of 78 g (0.5 mol) of *m*-methoxybenzyl chloride dissolved in 430 ml of anhydrous THF was added dropwise over a period of 55 min to a stirred suspension of 24.3 g (1 mol) of magnesium turnings in 100 ml of anhydrous THF at reflux temperature. The mixture was stirred for 30 min at reflux temperature then cooled to room temperature whereupon 2000 ml of anhydrous THF and 15.85 g (0.16 mol) of cuprous chloride were added and the mixture was stirred for 30 min at room temperature. A solution of 23.6 g (0.1 mol) of enone **1a** in 200 ml of anhydrous THF was then added with stirring over a 15-min period. When the addition was complete, the resulting suspension was poured into a stirred mixture of 1 *N* aqueous H_2SO_4 and ice. After stirring for 5 min, the mixture was worked up with ether. The resulting crude, oily product was then dissolved in 3000 ml of ethanol. Within 15 min, 600 ml of 10 *N* aqueous hydrochloric acid were added with stirring and cooling, the temperature not exceeding 20°. The faintly turbid solution was stirred at 20° for 4 hr and then allowed to stand at 0° for 12 hr. The solid was filtered with suction, washed with water, and dried at 80° (15 mm). Recrystallization from ethanol–ether gave 24.15 g (71%) of **4a**, mp 131–132°.

(1*S*, 3a*R*, 4*S*, 7a*S*)-(+)-1-*tert*-Butoxy-4-[2-(3-methoxyphenyl)ethyl]-7a-ethyl-3a,4,7,7a-tetrahydro-5(6*H*)-indanone (2b). Crude enone **1b**[1a] (5.01 g; 0.02 mol) was reacted with *m*-methoxybenzylmagnesium chloride using the procedure described in part B of the preceding experiment. The crude product (17.2 g) was chromatographed on 400 g of silica gel. Elution with 19:1 hexane–ether gave fractions yielding 9.4 g of an oil which was composed mainly of *m*-methylanisole and bis(*m*-methoxybibenzyl). The early fractions eluted with 9:1 hexane–ether afforded 3.16 g (42.5%) of the stable epimer **2b** [tlc: R_f 0.54 (system a); 0.10 (system b)] in essentially pure form as a viscous oil. A sample of this material was rechromatographed on silica gel and evaporatively distilled giving the analytical specimen as a viscous, pale-yellow oil: bp 160–180° (bath temperature) (0.2 mm); $[\alpha]^{25}D$ +11.93°; ir 1705 (C=O), 1600, 1585 cm^{-1} (anisole); uv max 217 nm (ε 7946), 272 (1980), 278 (1860); nmr δ 7.15 (m, 1, aromatic), 6.72 (m, 3, aromatic), 3.75 (s, 3, OCH_3), 3.48 (t, 1, *J* = 8 Hz, C_1–H), 1.12 ppm (s, O-*t*-C_4H_9); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.25; H, 9.85.

The later fractions eluted with 9:1 hexane–ether yielded 1.4 g (18.8%) of a mixture of **2b** (minor) and the 4*R* epimer of **2b** [major; tlc: R_f 0.45 (system a)]. This material was rechromatographed on silica gel. Later fractions eluted with 9:1 hexane–ether furnished 0.51 g of the essentially pure (tlc) 4*R* epimer of **2b** as a viscous, colorless oil: $[\alpha]^{25}D$ +17.96°; uv max 215 nm (ε 7970), 273 (1990), 279 (1870); ir 1700 (C=O), 1600, 1585 cm^{-1} (anisole); nmr δ 7.15 (m, 1, aromatic), 6.70 (m, 3, aromatic), 3.75 (s, 3, OCH_3), 3.43 (m, 1, C_1–H), 1.10 ppm (s, O-*t*-C_4H_9); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.53; H, 9.84.

A 54-mg sample of the 4*R* (axial) epimer was treated with 5 ml of a solution prepared by diluting 5 ml of 1 *N* aqueous NaOH to 50 ml with methanol. The mixture was heated for 5 min on a steam bath in order to effect solution. After cooling to room temperature, tlc analysis indicated that epimerization was complete as evidenced by the essential absence of the spot due to the more polar, 4-axial epimer. After standing at room temperature for 1.25 hr, the solution was diluted with dichloromethane and toluene then dried, filtered, and concentrated *in vacuo*. There was obtained 54 mg of colorless oil the tlc mobility of which was identical to that of **2b**. The latter substance was unchanged by alkali treatment.

(+)-17β-*tert*-Butoxy-13β-ethyl-3-methoxygona-1,3,5(10),9-(11)-tetraene (4b). A 7.28 g (19.6 mmol) sample of keto ether **2b** was cyclized using the procedure described above for the preparation of **4a**. There was obtained 5.86 g (84.5%) of colorless solid, mp 116–119° [tlc: one spot, R_f 0.34 (system b)]. A 1-g sample of this material was recrystallized from ethanol giving 0.91 g of colorless needles: mp 120–121°; $[\alpha]^{25}D$ +97.13°; uv max 263 nm (ε 19780), 298 (3150), infl 310 (2120); ir 1640 (C=C), 1615, 1580 (anisole), 1375 cm^{-1} (*t*-C_4H_9); nmr δ 7.45 (d, 1, *J* = 8 Hz, C_1–H), 6.63 (m, 2, C_2–H, C_4–H), 6.06 (m, 1, C_{11}–H), 3.73 (s, 3, OCH_3), 3.58 (m, 1, C_{17}–H), 1.14 ppm (s, O-*t*-C_4H_9); mass spectrum *m/e* 354 (M^+).

Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.37; H, 9.66.

(+)-17β-*tert*-Butoxy-3-methoxyestra-1,3,5(10)-triene (5a). A mixture of 0.8 g (2.35 mmol) of estratetraene **4a**, 0.25 g of 5% palladium on carbon, and 30 ml of ethyl acetate was stirred in an atmosphere of hydrogen for 1.33 hr. At the end of this time, 61 ml of hydrogen had been absorbed (59 ml theory). The catalyst was filtered with suction on Celite and the filter cake was washed with ethyl acetate. The filtrate and washes were combined and concentrated *in vacuo* giving 0.831 g of colorless oil which crystallized on standing at 0°. Recrystallization from ethanol yielded 0.433 g (54.2%) of **5a** as colorless crystals: mp 91–92.5°; ir 1610, 1580 (anisole), 1360 cm^{-1} (*t*-C_4H_9); uv max 277 nm (ε 2030), 285 (1900); nmr

δ 7.20 (d, 1, J = 8 Hz, C_1–H), 6.63 (m, 2, C_2–H, C_4–H), 3.73 (s, 3, OCH_3), 3.43 (t, 1, J = 8 Hz, C_{17}–H), 1.15 (s, O-t-C_4H_9), 0.75 ppm (s, 3, C_{13}–CH_3); mass spectrum m/e 342 (M^+). A sample of this material was sublimed at 110–120° (0.15 mm) prior to combustion analysis giving colorless solid: mp 90–92°; $[\alpha]^{25}D$ +62.20°.

Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.00. Found: C, 80.88; H, 9.91.

Tlc analysis (system b) of the mother liquor from the above recrystallization indicated an approximately 1:1 mixture of **5a** (R_f 0.39) and its 9β epimer (R_f 0.42).

(+)-17β-*tert*-Butoxy-13β-ethyl-3-methoxygona-1,3,5(10)-triene (5b). A 1-g (2.82 mmol) sample of gonatetraene **4b** was hydrogenated as in the preceding experiment. The crude product was chromatographed on 50 g of silica gel. Elution with 19:1 hexane–ether gave 0.925 g of colorless solid which was recrystallized from ethanol. This afforded 0.67 g (67%) of colorless plates: mp 121–123°; $[\alpha]^{25}D$ +44.69°; uv max 278 nm (ε 2020), 287 (1860); ir 1610, 1580 (anisole), 1360 cm^{-1} (t-C_4H_9); nmr δ 7.18 (d, 1, J = 9 Hz, C_1–H), 6.68 (m, 2, C_2–H, C_4–H), 3.74 (s, 3, OCH_3), 3.51 (t, 1, J = 8 Hz, C_{17}H), 1.15 ppm (s, O-t-C_4H_9); mass spectrum m/e 356 (M^+).

Anal. Calcd for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 80.71; H, 10.17.

(+)-3-Methoxyestra-1,3,5(10)-trien-17-one [(+)-Estrone 3-Methyl Ether] (7a). The crude product (**5a**) from hydrogenation (as described above) of 0.679 g (2 mmol) of estratetraene **4a** was dissolved in 10 ml of ice-cold trifluoroacetic acid.[9] The resulting yellow solution was kept at 0° for 20 hr then concentrated *in vacuo*. The residue was made alkaline with 0.5 N aqueous $KHCO_3$ solution (135 ml) and stirred at room temperature for 3 hr after the addition of 20 ml of tetrahydrofuran. Work-up with methylene chloride gave 0.773 g of 17-trifluoroacetoxy derivative which crystallized on standing: ir 1780 cm^{-1} (ester C=O). This product was dissolved in a mixture of 20 ml of methanol and 5 ml of 10% aqueous NaOH. The resulting solution was stirred at room temperature for 1 hr whereupon an additional 5 ml of 10% NaOH and 10 ml of methanol were added and stirring was continued for 1.75 hr. The mixture was then treated with brine and worked up with dichloromethane giving 0.567 g of crude estradiol 3-methyl ether (**6a**) as a pale-yellow foam: ir 3400 cm^{-1} (OH). Without purification, this material was dissolved in 20 ml of acetone and the solution was stirred with ice bath cooling while 0.65 ml of standard Jones reagent[11] was added over 3 min. After stirring for 5 min with ice bath cooling, the excess oxidant was decomposed by the addition of 2-propanol followed by ice–water. The acetone was removed at aspirator pressure and the residue was worked up with dichloromethane giving 0.537 g of crude **7a** as a yellow solid. Chromatography on 50 g of silica gel afforded 0.065 g of a more mobile impurity (colorless solid; eluted with 9:1 and 4:1 hexane–ether) followed by 0.35 g (61.7%) of essentially pure estrone 3-methyl ether (off-white solid; eluted with 4:1 and 2:1 hexane–ether). Recrystallization from acetonitrile gave colorless solid: mp 164–167°; $[\alpha]^{25}D$ +153.98° (c 1, dioxane); mmp with authentic (+)-estrone 3-methyl ether [$[\alpha]^{25}D$ +159.26° (c 1, dioxane)] 164–167.5°. The ir, uv, pmr, and mass spectra and tlc mobility (R_f 0.45; system d) were essentially identical with those of authentic (+)-estrone 3-methyl ether.

(+)-13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one (7b). A solution of 0.4 g (1.12 mmol) of pure **5b** and 0.1 g of p-toluenesulfonic acid monohydrate[9] in 10 ml of toluene was stirred and heated at reflux for 1 hr. The resulting solution was cooled and treated with saturated aqueous sodium bicarbonate solution then worked up with ether giving 0.348 g of (+)-17β-hydroxy-13β-ethyl-3-methoxygona-1,3,5(10)-triene (**6b**)[12,13] as a colorless solid.

This material was dissolved in 10 ml of acetone and the resulting solution was stirred with ice-bath cooling while 0.4 ml of Jones reagent[11] was added dropwise from a syringe over a 5-min period. After stirring at 0–5° for 2 min, the red mixture was decomposed by the addition of 10% aqueous $NaHSO_3$ solution. The resulting green mixture was diluted with water and worked up with ether giving 0.334 g of crude **7b** as a tan solid. This material was chromatographed on 20 g of silica gel. Fractions eluted with 4:1 hexane–ether afforded 0.274 g (82.3%) of colorless crystalline **7b**. Recrystallization from 1:1 cyclohexane–ethyl acetate furnished 0.207 g (62%) of colorless plates: mp 148.5–150°; $[\alpha]^{25}D$ +102.37° (c 1, $CHCl_3$), +102.82° (c 1, 1:1 $CHCl_3$–CH_3OH) [lit.[14] mp 147–149°; $[\alpha]D$ +110.9° ($CHCl_3$)] [lit.[13] mp 146–147°; $[\alpha]^{20}D$ +104° (c 1, 1:1 $CHCl_3$–CH_3OH)].

(+)-17β-Hydroxy-3-methoxyestra-1,3,5(10),6,8-pentaene (8a). A 1-g (2.94 mmol) sample of estratetraene **4a** was added to 10 ml of stirred, ice-cold trifluoroacetic acid. The resulting mixture was stirred with ice-bath cooling until the solid had completely dissolved then the green-brown solution was kept at 0° for 21.5 hr. The trifluoroacetic acid was removed under reduced pressure and the residue was treated with 40 ml of methanol and 10 ml of 10% aqueous NaOH. The alkaline mixture was warmed briefly on the steam bath then stirred at room temperature for 1.5 hr during which time a white precipitate formed. After removal of the methanol *in vacuo*, the mixture was diluted with water and worked up with ether giving 0.835 g of a yellow, semicrystalline residue: uv max 229 nm (ε 31410), 268 (3170), 277 (3750), 288 (2860), 309 (820), 323 (1170), 331 (1070), 338 (1320); mass spectrum m/e 282 (M^+ **8a**), 286 (M^+ **9a**). Tlc analysis (system a) showed two spots of approximately equal intensity R_f 0.15 (**9a**) and 0.10 (**8a**; R_f identical with that of authentic **8a**[16] prepared from d-equilenin). Gc analysis showed the elution of six components: retention time 9.4 (30.4%), 13.0 (9.9%), 14.5 (1.6%), 17.9 (56.6%), 21.7 (0.8%), and 24.9 min (0.7%). The peak with retention time of 13.0 min was shown to be identical with that exhibited by authentic estradiol 3-methyl ether by coinjection. The peak with retention time of 17.9 min was shown to be identical with that exhibited by authentic estrapentaene **8a**[16] by coinjection.

In another run, the crude alcohol mixture was chromatographed on 50 parts of silica gel. Elution with 9:1 benzene–ether gave material rich in **8a** which was recrystallized from methanol. This process yielded pure **8a** as colorless solid: mp 143–146°; $[\alpha]^{25}D$ +40.16° (c 1, dioxane) (lit.[16] mp 149–150°). The ir, pmr, and uv spectra were identical with those of an authentic sample of **8a** [mp 149–150° from methanol; $[\alpha]^{25}D$ +41.74° (c 1, dioxane)] prepared from d-equilenin by methylation followed by reduction with $LiAlH_4$.[16] The nmr spectra of both samples showed solvation by methanol. Tlc comparison of these samples showed identical R_f values of 0.35 (system d).

(+)-3-Methoxyestra-1,3,5(10),6,8-pentaen-17-one [(+)-Equilenin 3-Methyl Ether] (10a). The crude mixture of **8a** and **9a** obtained from 0.34 g (1 mmol) of estratetraene **4a** as described in the previous experiment was dissolved in 10 ml of acetone and the resulting solution was stirred and cooled in an ice bath while 0.5 ml of Jones reagent[11] was added dropwise. After stirring for 5 min the excess oxidant was decomposed with 2-propanol. The resulting mixture was treated with ice–water and most of the acetone was evaporated at reduced pressure. Work-up with chloroform (the chloroform extracts were additionally washed with saturated, aqueous $NaHCO_3$) gave 0.262 g of semicrystalline product. A combination of preparative thin layer chromatography (system c) and recrystallization from methanol gave 77.5 mg (27.6%) of colorless needles: mp 192–194°; the ir, uv, pmr, and mass spectra of which were identical with those of authentic (+)- equilenin 3-methyl ether [mp 195–196°; $[\alpha]^{25}D$ +82.64° (c 1, dioxane); prepared by methylation of d-equilenin[19]]. Another recrystallization from methanol gave colorless solid: mp 195–196°; $[\alpha]^{25}D$ +88.72° (c 0.86, dioxane) [lit.[16] mp 196–197°; lit.[19] mp 194–194.5°; lit.[20] mp 197–199°; $[\alpha]^{25}D$ +64° (c 1, $CHCl_3$)].

Mixture of Estratetraenols 11a and 12a. A solution of 1g (2.94 mmol) of estratetraene **4a** and 0.67 g (3.53 mmoles) of p-toluenesulfonic acid monohydrate in 80 ml of benzene was stirred and heated at reflux[9] for 1 hr. The reaction mixture was cooled, treated with saturated aqueous $NaHCO_3$, and worked up with ether giving 0.89 g of product as a yellow foam. This material was chromatographed on 50 g of silica gel. Elution with 1:1 hexane–ether furnished 0.698 g (83.6%) of a pale-yellow solid composed mainly of the mixture of **11a** and **12a** (approximately 5:3, respectively by nmr analysis); uv max 264 nm (ε 15750); infl 213 (19500), 272 (14000), 309 (2500), 322 (500); ir 3600 (OH), 1600 cm^{-1} (anisole); nmr δ 7.53 [d, J = 9 Hz, C_1–H of **11a** (major)], 7.13 [d, J = 9 Hz, C_1–H of **12a** (minor)], 6.66 (m, 2, C_2–H, C_4–H), 6.11 [m, ~ 0.65, C_{11}–H (**11a**)], 3.77 (s, OCH_3), 0.80 [s, C_{13}–CH_3 of **11a** (major)], 0.77 ppm [s, C_{13}–CH_3 of **12a** (minor)]; mass spectrum m/e 284 (M^+). Six peaks were eluted on gc analysis: retention time 9.8 (0.9%), 12.2 (8.7%), 14.7 (83.6%), 17.9 (2.6%), 19.0 (2.6%), 24.0 min (1.6%). The peak with retention time of 17.9 min was shown to be due to estrapentaene **8a** by coinjection. The peak with retention time of 14.7 min was due to the mixture of estratetraenes **11a** and **12a** which was not resolved. The remaining peaks were not identified.

Acknowledgment. We wish to express our gratitude to the personnel of the Physical Chemistry Department of Hoffmann-La Roche Inc., Nutley, N.J., for carrying out many of the spectral, microanalytical, and polarimetric determinations required in this work.

Registry No.—**1a,** 53052-87-2; **1b,** 53052-91-8; **2a,** 53016-36-7; **2b,** 53052-90-7; **2b** 4*R*-epimer, 53052-89-4; **3a,** 53684-32-5; **4a,** 53053-33-1; **4b,** 53053-35-3; **5a,** 53053-36-4; **5a** trifluoroacetoxy derivative, 29755-34-8; **5b,** 53053-37-5; **6a,** 1035-77-4; **6b,** 3625-82-9; **7a,** 1624-62-0; **7b,** 848-04-4; **8a,** 15375-29-8; **9a,** 53776-51-5; **10a,** 3907-67-3; **11a,** 6702-61-0; **12a,** 6733-79-5; *m*-methoxybenzyl chloride, 824-98-6.

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Synthesis of 9,11-Secoestradiol 3-Methyl Ether

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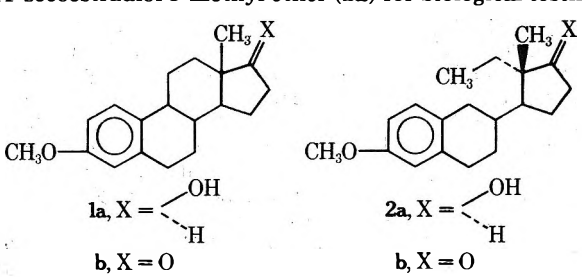
Received October 9, 1974

Estradiol 3-methyl ether (**1a**) is known to possess both estrogenic and antifertility activity. In an attempt to enhance the antifertility activity and/or diminish the estrogenic activity 9,11-secoestradiol 3-methyl ether (**2a**) has been prepared via a seven-step sequence starting with **1a.** Compound **2a** had weak estrogenic and antifertility activity with no appreciable separation of activities.

Several articles dealing with 9,11-seco steroids have appeared in the recent literature. Crossley and Dowell[1] reported the synthesis of 9,11-secoprogesterone in an attempt to prepare a derivative having modified progestational activity. Brain and coworkers[2] prepared a series of 9,11-seco steroids having both the A and B rings aromatic via total synthesis. We have previously reported the synthesis of optically active 9,11-seco steroids derived from estradiol 3-methyl ether (**1a**)[3] as well as the synthesis of 9,11-seco steroids derived by total synthesis.[4] As an extension of our earlier work[3] we were interested in preparing 9,11-secoestradiol 3-methyl ether (**2a**) for biological testing.



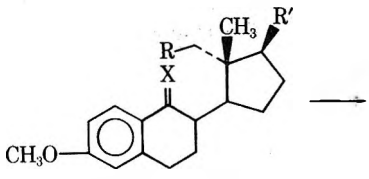
Since estradiol 3-methyl ether (**1a**) is known to possess both estrogenic[5] and antifertility[6] activity, we had hoped that cleavage of the 9,11 bond would enhance the antifertility activity, thereby leading to a greater separation of activities via the "entropy effect."[7]

The key intermediate in our previous series, 17β-hydroxy-3-methoxy-9-oxo-9,11-secoestra-1,3,5(10)-trien-11-oic acid 17-acetate (**3a**), appeared to be an ideal starting material for the synthesis of **2a.** Compound **3a** was prepared by the procedure of Cambie[8] and was purified by column chromatography. The homogeneity of **3a** was established by NMR and thin layer chromatography (TLC). The nmr spectrum of **3a** exhibited sharp singlets at δ 1.08 for the C-18[9] methyl and 1.97 for the acetoxy methyl. If compound **3a** had undergone partial epimerization at C-8 during its preparation, one would expect that the C-18 methyls and/or the acetoxy methyls of the two epimers would have different field positions in the NMR. The only resonances attributable to the C-18 methyl and the acetoxy methyl are the sharp singlets previously mentioned. The homogeneity of **3a** was further confirmed by examining the fully proton decoupled ^{13}C NMR spectrum which contained 20 sharp resonances.[10] If the compound had been a mixture of isomers, some of the carbon atoms would have been nonequivalent and more than 21 peaks would have been observed in the spectrum. Since it is highly unlikely that **3a** had undergone complete epimerization at C-8 during the ring cleavage reaction, we conclude that the stereoconfiguration at C-8 is the same as that in estradiol 3-methyl ether.

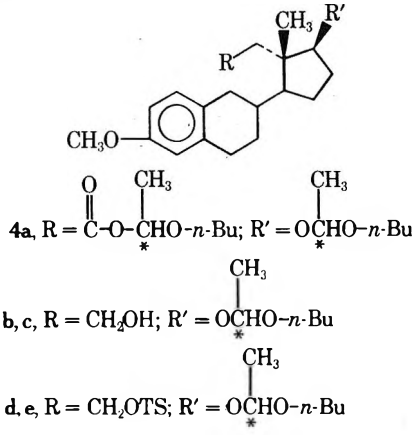
In the synthesis of 9,11-secoprogesterone,[1] the 9-keto and the 11-carboxy functions were removed concurrently by successively reducing each to the corresponding alcohol,

converting the resultant diol into a dimesylate, and displacing the mesylate groups with lithium aluminum hydride. In the synthesis of **2a** we chose to accomplish this series of transformations in a stepwise manner (Scheme I).

Scheme I



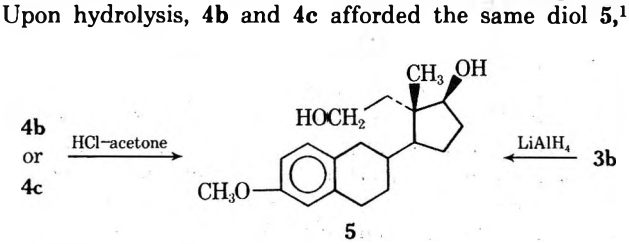
3a, R = COOH; R′ = OAc; X = O
b, R = COOH; R′ = OAc; X = H_2
c, R = COOH; R′ = OH; X = H_2



4a, R = C(=O)-O-CHO-*n*-Bu; R′ = OCHO-*n*-Bu
b, c, R = CH_2OH; R′ = OCHO-*n*-Bu
d, e, R = CH_2OTS; R′ = OCHO-*n*-Bu

The ketone function at C-9 in compound **3a** was cleanly removed by hydrogenolysis over palladium-on-carbon in ethanol at 50°. In an attempt to determine whether epimerization occurs at C-8 during the reduction compound **3a** was subjected to the reaction conditions in the absence of hydrogen. The ir and NMR spectra, as well as the optical rotation, of the recovered material were virtually identical with that of **3a**, indicating that the compound does not epimerize at C-8 prior to reduction. The fact that a chromatographically homogeneous product, **3b**,[11] was isolated in 78% yield further indicates that epimerization does not occur during the reduction. Although the possibility of complete epimerization occurring during the reduction cannot be ruled out on the basis of our experiments, we feel that such a possibility is highly unlikely.

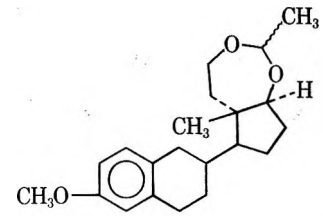
The conversion of **3b** into **2a** was relatively straightforward. Hydrolysis of **3b** with methanolic KOH afforded the alcohol **3c**. Treatment of **3c** with butyl vinyl ether gave **4a** which reacted in situ with lithium aluminum hydride to afford a pair of diastereomeric butyl vinyl ether derivatives **4b,c** which were separable by column chromatography. Upon hydrolysis, **4b** and **4c** afforded the same diol **5**,[12]



5

thereby indicating that **4b** and **4c** were isomeric at the newly introduced chiral center resulting from the reaction of the 17β-hydroxy group with butyl vinyl ether.

Treatment of the mixture of **4b,c** with *p*-toluenesulfonyl chloride afforded the tosylates **4d,e** which were used without further purification for the next step. The synthesis of



6

2a was completed by displacing the tosylate group with lithium aluminum hydride followed by acid hydrolysis of the protecting group at C-17. A small amount of an impurity believed to be the cyclic acetal **6** was isolated during the purification of **2a**. Compound **6** is presumed to arise via loss of *n*-butyl alcohol from **4b,c** during the formation of **4d,e**.

Conversion of **2a** into 9,11-secoestrone 3-methyl ether (**2b**) by treatment with Jones reagent further suggests that the assigned structure of **2a** is correct. We speculated that if **2a** has the same stereochemistry as estradiol 3-methyl ether (**1a**), then the difference in molecular rotations[13] between **2a** and **2b** should be of the same magnitude and direction as the difference between the rotations of **1a** and estrone 3-methyl ether (**1b**).[14] The molecular rotations for **1a** and **1b** are +220 and +437, respectively. Therefore, the expected value for **2b** would be 217 more than the value of +193 for **2a**. The observed value of +423 for compound **2b** is in excellent agreement with the predicted value of +410. However, since cleavage of the 9,11 bond of the steroid nucleus gives rise to free rotation about the 8,14 bond, application of the "method of molecular-rotation differences" may not be entirely valid in this instance and our results may indeed be only coincidental.

Compound **2a** was found to have 0.30% the estrogenic activity[5] of estradiol 3-methyl ether (**1a**). A comparison of the antifertility activities[6] revealed that **2a** had an ED_{50} of 450 μg vs. an ED_{50} of 2.5 μg for **1a**. Hence, cleavage of the 9,11 bond resulted in a marked reduction of the estrogenic and antifertility activities. Little, if any, separation of activities was achieved.

Experimental Section

Melting points were determined on a Fisher-Johns melting block and are uncorrected. Infrared spectra were recorded on a Beckman IR-12 grating spectrophotometer. NMR spectra were obtained in $CDCl_3$ on a Varian A-60 or T-60 or XL-100 spectrometer using tetramethylsilane as internal standard. Specific rotations were obtained in chloroform (c 1.0) using a Perkin-Elmer (Model 141) polarimeter. Elemental analyses were performed by the microanalytical group at Searle Laboratories.

Purification of 3a. A sample of **3a** prepared by the procedure of Cambie[8] was chromatographed on SilicAR CC-4 using benzene and EtOAc as eluents. Pure **3a** was obtained in the 20 and 40% EtOAc fractions and was recrystallized from benzene–Skellysolve B to give a white solid: mp 148–150°; $[\alpha]^{25}D$ −13°; ir (KBr) 1745 [OC(=O)CH_3], 1730 (COOH), and 1680 cm^{-1} (conjugated ketone); NMR δ 1.10 (s, CH_3), 1.98 [s, OC(=O)CH_3], 3.86 (s, OCH_3).

(1*S*,2*S*,2′*R*,5*S*)-2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-5-hydroxy-1-methylcyclopentaneacetic Acid Acetate (3b). A solution of **3a** (4.54 g, 12.1 mmol) in 250 ml of EtOH was hydrogenated over 5% Pd-on-carbon (0.5 g) at 50° for 72 hr in a Parr shaker. The solution was filtered and the solvent was removed in vacuo to give 4.37 g of a yellow oil which crystallized upon standing. The product was chromatographed on 90 g of SilicAR CC-4 to give **3b** in the 10% EtOAc–90% benzene fractions. Recrystallization from EtOAc–Skellysolve B gave **3b** (3.40 g, 78%): mp 125–127°; $[\alpha]^{25}D$ +50°; NMR δ 1.03 (s, CH_3), 2.02 [s, OC(=O)CH_3], 3.76 (s, OCH_3).

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.64; H, 7.84.

Control Experiment on 3a. A solution of **3a** (0.454 g, 1.21 mmol) in 25 ml of EtOH containing 0.050 g of Pd-on-carbon was heated at 50° for 72 hr under nitrogen. The solution was filtered

and the solvent was removed in vacuo to give 0.450 g of an oil which crystallized upon standing. The ir and NMR spectra as well as the optical rotation on the recovered material were virtually identical with those of **3a**: $[\alpha]^{22}D$ −11°; NMR δ 1.10 (s, CH_3), 1.99 [s, $OC(=O)CH_3$], 3.87 (s, OCH_3).

(1*S*,2*S*,2′*R*,5*S*)-2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-5-hydroxy-1-methylcyclopentaneacetic Acid (3c). A solution of **3b** (3.33 g, 9.25 mmol) in 50 ml of CH_3OH was treated with a solution of KOH (3.00 g, 53.5 mmol) in 15 ml of water, and the solution was refluxed for 2 hr. The solution was diluted with 250 ml of water, filtered, and acidified with hydrochloric acid. The solid which formed was collected and thoroughly washed with water. Recrystallization from EtOAc–Skellysolve B gave **3c** (2.65 g, 90%): mp 141.5–142.5°; $[\alpha]^{23}D$ +65°; NMR δ 0.97 (s, CH_3), 3.76 (s, OCH_3).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.35; H, 8.35.

Conversion of 3c into 4b,c. A solution of **3c** (2.57 g, 8.09 mmol) in 15 ml of THF was treated with *n*-butyl vinyl ether (1.70 g, 17.0 mmol) and 3 drops of a 10% solution (v/v) of methanesulfonic acid in THF. After stirring at room temperature for 4 hr, no further reaction could be detected by TLC (20% EtOAc–80% benzene). The crude mixture was added dropwise to a stirred suspension of $LiAlH_4$ (0.500 g, 13.2 mmol) in 20 ml of THF and the mixture was stirred at room temperature for 24 hr. The mixture was carefully hydrolyzed by the dropwise addition of 2.0 ml of 5% NaOH solution. The mixture was diluted with 50 ml of ether and filtered. The inorganic salts were thoroughly washed with ether and the combined organic phases were concentrated in vacuo. TLC (20% EtOAc–80% benzene) indicated the presence of two compounds, **4b,c** in a ratio of 1:1 along with a lesser amount of **5**. The crude mixture was chromatographed on 90 g of SilicAR CC-7 using EtOAc and benzene as eluents and taking 40-ml fractions. Compound **4b** (1.27 g, 39%) was obtained pure in the 2% and early 5% EtOAc–benzene fractions. A mixture of **4b,c** (0.513 g, 16%) was obtained in the later 5% and early 10% EtOAc–benzene fractions. Compound **4c** (1.07 g, 33%) was obtained pure in the later 10 and 20% EtOAc–benzene fractions. Compound **5** (0.247 g, 8%) was obtained in the 100% ethyl acetate fractions. Recrystallization from benzene afforded 0.170 g of **5**, mp 151–152°, $[\alpha]^{23}D$ +58°. Compound **5** was virtually identical with an authentic sample prepared from **3b**.

(1*S*,2*S*,2′*R*,5*S*)-2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-5-hydroxy-1-methylcyclopentaneethanol (5). A solution of **3b** (0.780 g, 2.17 mmol) in ether (10 ml)–THF (5 ml) was added dropwise to a stirred slurry of $LiAlH_4$ (0.420 g, 11.1 mmol) in 400 ml of ether, and the mixture was stirred at room temperature for 18 hr. The mixture was hydrolyzed by the dropwise addition of 1.7 ml of 5% NaOH solution. The mixture was diluted with 40 ml of CH_2Cl_2 and filtered. The solvent was removed in vacuo to give a white solid which was recrystallized from benzene–Skellysolve B to give 5 (0.585 g, 89%): mp 151–153°; $[\alpha]^{24}D$ +62°; NMR δ 0.87 (s, CH_3), 3.74 (s, OCH_3).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.91; H, 9.27.

Hydrolysis of 4b. A solution of **4b** (0.136 g, 0.336 mmol) in 5 ml of acetone and 1 ml of water was treated with 4 drops of concentrated HCl, and the solution was stirred for 30 min. The product was precipitated by adding 15 ml of water and saturating the solution with NaCl. The product was collected, air dried, and recrystallized from benzene–Skellysolve B to give **5** (0.0681 g, 67%), mp 151.5–153.5°, $[\alpha]^{23}D$ +63°. The compound was virtually identical with an authentic sample of **5** prepared from **3b**.

Hydrolysis of 4c. A sample of **4c** (0.107 g, 0.290 mmol) was treated in the same manner as **4b** to give a product which was recrystallized from benzene–Skellysolve B to give **5** (0.0454 g, 52%), mp 151–153°, $[\alpha]^{23}D$, +61°. The compound was virtually identical with an authentic sample of **5** prepared from **3b**.

Conversion of 4b,c to 4d,e. A solution of **4b,c** (2.59 g, 6.40 mmol) in 20 ml of pyridine was treated with *p*-toluenesulfonyl chloride (2.46 g, 12.8 mmol) and the reaction mixture was placed in a refrigerator for 42 hr. The mixture was poured onto 200 ml of water, stirred for 15 min, and extracted with ether. The extracts were dried over anhydrous Mg_2SO_4 and filtered. The solvent was removed in vacuo to give 3.83 g of an oil[15] which was used without further purification.

(1*S*,2*S*,2′*R*,3*S*)-2-Ethyl-2-methyl-3-(1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)cyclopentanol (2a). A solution of **4d,e**[15] (3.83 g, 6.86 mmol) in 30 ml of THF was added dropwise to a stirred suspension of $LiAlH_4$ (2.00 g, 52.8 mmol) in 70 ml of THF and the mixture was refluxed for 18 hr. The mixture was diluted with 50 ml of ether and hydrolyzed by the dropwise addition of 8 ml of a 10% NaOH solution. The solution was filtered and the inorganic salts were thoroughly washed with ether. The organic solvents were removed in vacuo to give 2.61 g of an oil which was dissolved in 50 ml of acetone and 10 ml of water and treated with 1 ml of concentrated HCl. After stirring for 90 min, the mixture was diluted with 500 ml of water and extracted with ether. The extracts were dried over anhydrous Mg_2SO_4 and filtered. The solvent was removed in vacuo to give 1.72 g of an oil which was chromatographed on 90 g of SilicAR CC-7 using EtOAc and benzene as eluents and taking 40-ml fractions. Compound **6** (0.087 g, 4%) was obtained in the first few benzene fractions. Compound **2a** (1.29 g, 70%) was eluted with 10% EtOAc–90% benzene. Recrystallization from pentane afforded 1.07 g of **2a**: mp 42–43.5°; $[\alpha]^{25}D$ +67°; NMR δ 0.83 (s, CH_3), δ 0.88 (t, J = 7 Hz, CH_3), 3.77 (s, OCH_3).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.87; H, 9.67.

(2*S*,2′*R*,3*S*)-2-Ethyl-2-methyl-3-(1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)cyclopentanone (2b). A solution of **2a** (0.400 g, 1.39 mmol) in 30 ml of acetone was cooled to 0°, and excess Jones reagent was added dropwise until the orange color persisted for 10 min. The excess reagent was destroyed by the dropwise addition of isopropyl alcohol and the reaction mixture was diluted with 100 ml of water and extracted with ether. The extracts were dried over anhydrous Mg_2SO_4 and filtered. Solvent removal gave a yellow oil which was chromatographed on 30 g of SilicAR CC-7 using Skellysolve B and benzene as eluents. The product was eluted in the benzene fractions and the solvent was removed in vacuo to give 0.337 g of an oil which crystallized upon standing. Recrystallization from pentane afforded **2b** (0.300 g, 75%): mp 77.5–79.5°; $[\alpha]D$ +148°; NMR δ 0.96 (s, CH_3), 0.74 (t, J = 7 Hz, CH_3), 3.80 (s, OCH_3).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.89; H, 9.25.

Acknowledgment. The authors gratefully acknowledge the technical assistance of Mr. Bipin Desai, Mrs. Karlene Salamon, and Miss Bobbie Coleman in the preparation of some of the seco steroids, of Mr. William Selby and his staff for optimizing the yield in the hydrogenolysis reaction, of Mr. Wally Pautsch and his staff in the biological evaluation of the compounds, and of Miss Patricia Green for interpreting and assigning the resonances in the noise decoupled ^{13}C NMR spectrum of **3a**.

Registry No.—**2a**, 53940-71-9; **2b**, 53940-72-0; **3a**, 1247-46-7; **3b**, 53940-73-1; **3c**, 53940-74-2; **4b**, 53940-75-3; **4c**, 54003-03-1; **4d**, 53940-76-4; **4e**, 53990-65-1; **5**, 53940-77-5.

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(8) R. C. Cambie and T. D. R. Manning, *J. Chem. Soc. C*, 2603 (1968).
(9) The steroid numbering system has been used throughout the text of this paper for convenience.
(10) Since compound **3a** contains 21 carbons, the presence of only 20 resonances in the decoupled spectrum indicates that two of the carbon atoms, most likely C-6 and C-7, are magnetically equivalent.
(11) Compound **3b** was purified by column chromatography (see Experimental Section) to remove trace amounts of unreacted **3a** as well as trace amounts of a more polar material believed to be the 9-hydroxy intermediate.
(12) An authentic sample of **5** was prepared by treating **3b** with lithium aluminum hydride.
(13) The "method of molecular-rotation differences" has had many successful applications in the steroid field. For a summary, see D. H. R. Barton and W. Klyne, *Chem. Ind. (London)*, 755 (1948).
(14) Samples of **1a** and **1b** were obtained from Searle Chemicals Inc. The specific rotations are $[\alpha]^{25}D$ +77° and $[\alpha^{25}D$ +154°, respectively.
(15) The sample contained a small amount of pyridine. Theory requires 3.57 g, 6.40 mmol.

Epimerization of Bis(α-phenylethyl) Ether and 2-Octyl α-Phenylethyl Ether

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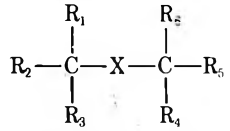
Received May 28, 1974

Epimerization of bis(α-phenylethyl) ether and 2-octyl α-phenylethyl ether catalyzed by boron trifluoride etherate was investigated in aprotic solvents. Bis(α-phenylethyl) ether gave a mixture consisting of 89.0% *dl* and 11.0% meso isomers in carbon tetrachloride and a mixture consisting of 78.8% *dl* and 21.2% meso isomers in liquid sulfur dioxide. On the other hand, 2-octyl α-phenylethyl ether gave a mixture consisting of 58.7% threo and 41.3% erythro isomers in the former solvent and a mixture consisting of equal amounts of threo and erythro isomers in the latter.

Many studies have been reported on epimerization of pyranose[1-3] and other ring compounds.[4-7] In epimerization reactions of simple diastereomers[8-10] having structure 1



1, X = CH_2 or SO_2

difference in thermodynamical stabilities between two isomers is not so large as that in the ring compounds. In the epimerization study of 2,4-diphenylpentane Williams, *et al.*, have obtained slightly more *dl* isomer than meso isomer.[9] On the other hand, the results obtained by Bordwell, *et al.*,[10] in epimerization of α-methylbenzyl sulfone were shown to be opposite to the former results by Meyers and Malte.[11]

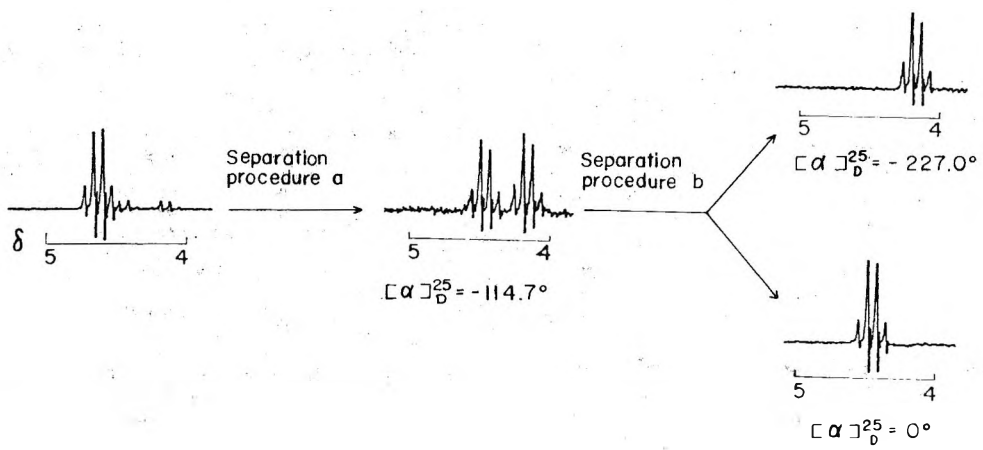
The present study reports that in epimerization of bis(α-phenylethyl) ether the *dl* isomer is notably more stable than the meso isomer under certain experimental conditions.

Results

Configurational Assignment of *dl*- and *meso*-Bis(α-phenylethyl) Ether. We have made a configurational assignment of ethers isolated from a liquid sulfur dioxide solution of (−)-α-phenylethyl alcohol (I) on the basis of their optical rotation data as described below. As reported in the preceding paper,[12] the optical rotation of liquid sulfur dioxide solution of the alcohol (I) changes slowly. The methine proton signal pattern in the nmr spectra of the reaction solution was also found to change as shown in Figure 1, and the optically inactive solution afforded optically inactive bis(α-phenylethyl) ether (II). A comparison of the nmr spectra of the reaction solution and authentic samples indicates that one quartet at lower field and two quartets at higher field are attributable to methine protons of I and II, respectively, and in the early stage of the reaction about equal amounts of two isomers of ether have formed. Chemical shift values of the methine proton of the alcohol in Figure 1 are somewhat different from each other probably because of the concentration effect on hydrogen bond formation of the hydroxyl group. These isomers of ether were isolated separately from the 25-min reaction mixture (*cf.* Figure 1, b) by the procedure shown in Scheme I. One ether with a methine signal at higher field had specific rotation of −227.0° and therefore was assigned the optically active configuration of *dl* isomer, and the other with a methine signal at lower field was optically inactive and was assigned the meso configuration. These assignments are in good accord with that made for α-methylbenzyl sulfide.[11] In glc of the isomers, the one with methine proton signals at higher field in its nmr spectrum had shorter retention time.

Epimerization of Bis(α-phenylethyl) Ether. The result of epimerization of (−)-bis(α-phenylethyl) ether with benzoyl peroxide in liquid sulfur dioxide is shown in Figure 2. The product was a mixture of ethers consisting of 78.4% *dl* and 21.6% meso isomers, and the elimination reaction was scarcely observed. Epimerization catalyzed by boron trifluoride etherate (0.0045 mol/l.) at 25° was accomplished in a few minutes giving a mixture consisting of 78.8% *dl* and 21.2% meso isomer and at more prolonged reaction time elimination followed by polymerization took place to

Scheme I



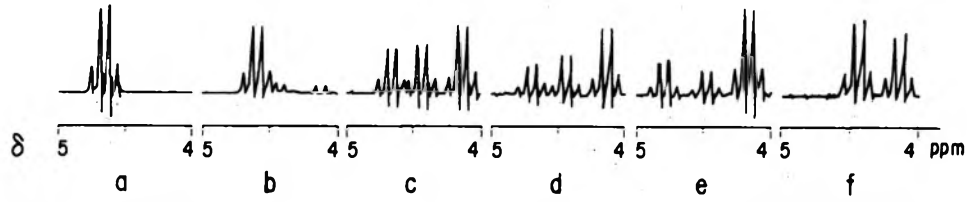


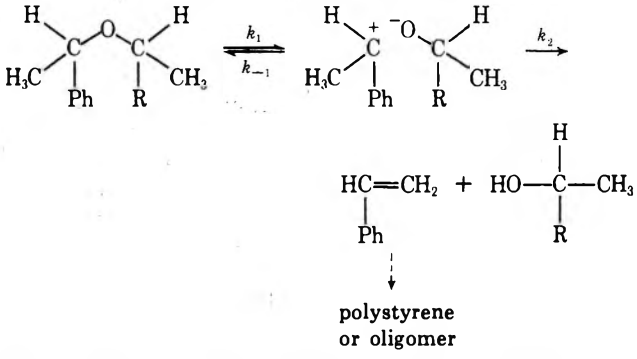
Figure 1. The nmr spectra (100 MHz) of methine protons of residual liquid obtained by evaporation of SO_2 from liquid sulfur dioxide solution of (−)-α-phenylethyl alcohol (0.40 mol/l.) (solvent, carbon tetrachloride): a, authentic (±)-α-phenylethyl alcohol; b, products obtained after 31 min; c, after 95 min; d, after 240 min; e, after 4 days; f, authentic bis(α-phenylethyl) ether.

give polystyrene, and in a few hours the ether completely disappeared. Epimerization in carbon tetrachloride with boron trifluoride etherate proceeded slowly as shown in Figure 3, and addition of more catalyst (0.065 mol/l.) caused decomposition of large amounts of ether. In both cases, however, ratios of *dl* and meso ether formed were almost the same. Results of epimerization reactions in other aprotic solvents are shown in Table I. Each run of the reaction was allowed to continue until the ratio of ethers was constant.

Epimerization of 2-Octyl α-Phenylethyl Ether. 2-Octyl α-phenylethyl ether which was prepared from sodium 2-octoxide and α-phenylethyl chloride was a mixture consisting of about equal amounts of two isomers separable by glc. The facts that retention time of one of the two isomers is shorter than that of the other isomer, and the methine proton signal in the nmr spectrum (Figure 4) of the former absorbs at higher field than that of the latter allow to assign tentatively the isomer 1 to be threo and the isomer 2 erythro from comparison of the glc and nmr behavior of these isomers and bis(α-phenylethyl) ether. Results of epimerization catalyzed by boron trifluoride etherate of 2-octyl α-phenylethyl ether in carbon tetrachloride or liquid sulfur dioxide are summarized in Figures 5 and 6 and Table II. Epimerization of this ether was not effected in the presence of benzoyl peroxide in liquid sulfur dioxide.

Discussion

The mechanism of the epimerization and elimination reaction is illustrated as follows.



In the reaction starting with 2-octyl α-phenylethyl ether (R = *n*-hexyl), the amount of 2-octyl alcohol formed indicates that no further dehydration took place. On the other hand, bis(α-phenylethyl) ether afforded almost no corresponding alcohol, probably because the α-phenylethyl alcohol formed has changed to styrene or polystyrene in the reaction catalyzed by boron trifluoride etherate. Epimerization of ether is attributed to the ionization process (k_1) and ion-pair return process (k_{-1}). Epimerization of bis(α-phenylethyl) ether in liquid sulfur dioxide in the presence of benzoyl peroxide was completed without the elimination reaction within a few days and on standing for several weeks the elimination reaction took place. In the epimerization reaction catalyzed by boron trifluoride etherate polysty-

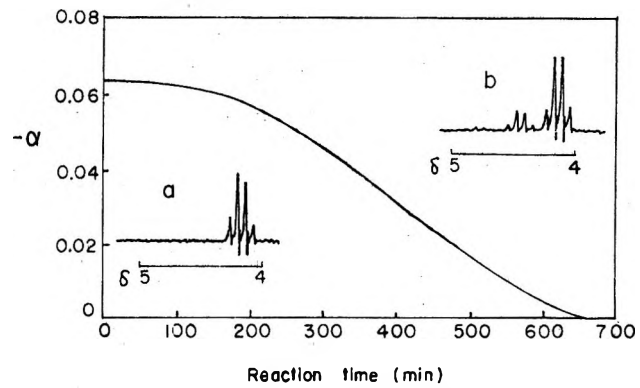


Figure 2. Epimerization of (−)-bis(α-phenylethyl) ether in liquid sulfur dioxide at 25°. Nmr methine proton signals of (a) starting material and (b) the product are shown. Ether ($[\alpha]^{25}D$ −227.0°, 6.4 mg) in 2.23 ml of SO_2; benzoyl peroxide, 2.22×10^{-2} mol/l.; cell length, 0.097 dm; wavelength, 589 nm.

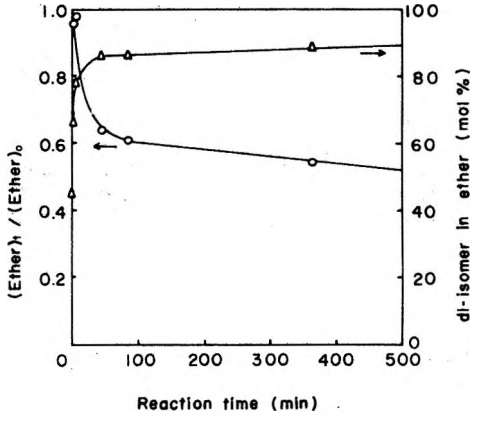


Figure 3. Epimerization and elimination of bis(α-phenylethyl) ether in carbon tetrachloride at 25°. Ether consisting of 45.4% *dl* and 54.6% meso isomers was used (0.05 mol/l.); BF_3OEt_2, 0.012 mol/l. ○, decrease of ether; △, mol % of *dl* isomer in ether.

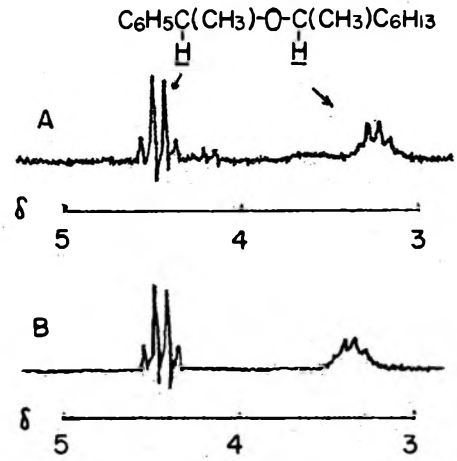


Figure 4. The nmr spectra (100 MHz) of methine protons of 2-octyl α-phenylethyl ether (in carbon tetrachloride): (A) isomer 1; (B) isomer 2.

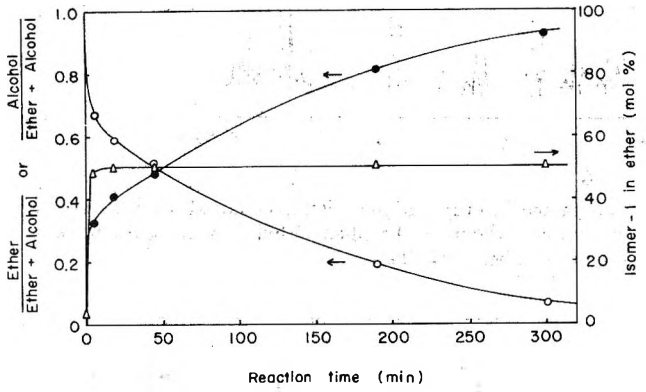


Figure 5. Epimerization and elimination of 2-octyl α-phenylethyl ether in liquid sulfur dioxide at 25°. Ether consisting of 3% isomer 1 and 97% isomer 2 was used (0.032 mol/l.); BF_3OEt_2, 0.0044 mol/l. O, mol fraction of ether; ●, mol fraction of 2-octanol; △, mol % of isomer 1 in ether.

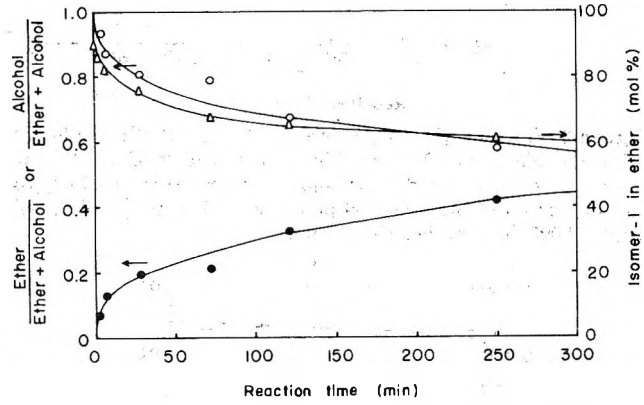


Figure 6. Epimerization and elimination of 2-octyl α-phenylethyl ether in carbon tetrachloride at 25°. Ether consisting of 90% isomer 1 and 10% of isomer 2 was used (0.029 mol/l.); BF_3OEt_2, 0.025 mol/l. O, mol fraction of ether; ●, mol fraction of 2-octanol; △, mol % of isomer 1 in ether.

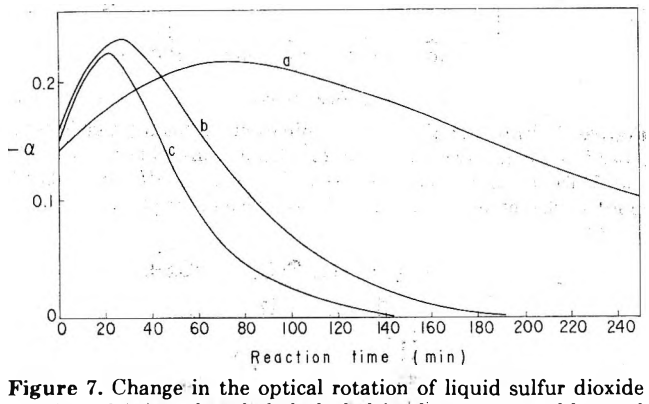


Figure 7. Change in the optical rotation of liquid sulfur dioxide solution of (−)-α-phenylethyl alcohol in the presence of benzoyl peroxide (BPO) at 25°: a, alcohol 2.83×10^{-2} mol/l., BPO 2.46×10^{-3} mol/l.; b, alcohol 2.94×10^{-2} mol/l., BPO 3.90×10^{-2} mol/l.; c, alcohol 2.79×10^{-2} mol/l., BPO 1.13×10^{-1} mol/l. Cell length, 0.85 dm; wavelength, 589 nm.

rene or its oligomer formed. Schulz and Vanihashemi observed cationic polymerization of styrene catalyzed by peroxide in liquid sulfur dioxide, which they attributed to acid catalysis formed from the reagents.[13] As shown in Figure 7 benzoyl peroxide accelerated the change in optical rotation of liquid sulfur dioxide solution of (−)-α-phenylethyl alcohol. Probably in the present study benzoyl peroxide gave weak acid catalysis in liquid sulfur dioxide. Even in the absence of benzoyl peroxide epimerization occurred very slowly in liquid sulfur dioxide. It is not clear what species catalyzed in this case. Since acid catalyst formed from benzoyl peroxide and liquid sulfur dioxide is weaker than boron trifluoride etherate, the ion-pair return process (k_{-1}) would predominate over the elimination process (k_2) in the reaction catalyzed by peroxide. Kice[14,15] and Goering[16] and their coworkers have discussed the solvent effects on ion-pair return.

Table I
Composition of Ether Obtained by Epimerization of Bis(α-phenylethyl) Ether at 25°

Solvent	Conditions: Ether (mol/l.)	Conditions: BF_3OEt_2 (mol/l.)	Conditions: Reaction time	Composition of ether, %: *dl* isomer	Composition of ether, %: meso isomer
Carbon tetrachloride	0.05	0.012	20 hr	89.0	11.0
n-Hexane	0.099	0.017	4 days	87.7	12.3
Liquid sulfur dioxide	0.033	0.0045	2 min	78.8	21.2
Nitrobenzene	0.094	0.019	20 hr	68.1	31.9

Table II
Composition of Ether Obtained by Epimerization of 2-Octyl α-Phenylethyl Ether at 25°

Solvent	Conditions: Ether (mol/l.)	Conditions: BF_3OEt_2 (mol/l.)	Conditions: Reaction time	Composition of ether, %: Isomer 1	Composition of ether, %: Isomer 2
Carbon tetrachloride	0.029	0.025	20 hr	58.7	41.3
Liquid sulfur dioxide	0.032	0.0044	5 hr	50.0	50.0

Data in Tables I and II indicate that *dl* or threo isomer is more stable than meso or erythro isomer, respectively, in aprotic solvent. Williams, *et al.*, reported that epimerization of 2,4-diphenylpentane in dimethyl sulfoxide gave a mixture consisting of 51.5% *dl* and 48.5% meso isomers.[9] Since the C–O bond is shorter than the C–C bond, steric interaction between substituents may be pronounced in ether compared to 2,4-diphenylpentane. Bordwell and coworkers reported that the epimerization of α-methylbenzyl sulfone in methanol gave a mixture consisting of 55.6% mp 140° isomer and 44.4% mp 89° isomer,[10] to which Meyers and Malte assigned the meso and *dl* configuration, respectively.[11] The difference between the ratio of ethers obtained by epimerization of α-methylbenzyl sulfone and that of bis(α-phenylethyl) ether may depend on two factors, *i.e.*, the existence of the sulfonyl group in α-methylbenzyl sulfone and the difference in the bond length between the C–S and C–O bond. However, the notable stability of the *dl* isomer compared to meso isomer in bis(α-phenylethyl) ether is not well explained only on the basis of these factors. If a special interaction between two phenyl groups in bis(α-phenylethyl) ether is considered, the notably stability of the *dl* isomer compared to the meso isomer is explained. Tables I and II indicate that change from *n*-hexyl to phenyl groups caused a remarkable difference in the results. This remarkable difference may be caused by two factors, *i.e.*, the dif-

ference in the special interaction (*viz.* phenyl–phenyl, *n*-hexyl-phenyl) and the difference in the flexibility between phenyl and *n*-hexyl groups.

Solvent effects in the ratio of ethers obtained are shown in Tables I and II. In the epimerization reactions carried out in less polar solvent, *i.e.*, *n*-hexane or carbon tetrachloride, remarkable difference in the ratio of two isomers formed is observed. Presumably, steric interaction is mitigated because of solvation.

Experimental Section

(−)-α-Phenylethyl Alcohol. Material prepared according to the method of Pickard and Kenyon[17] had specific rotation ($[\alpha]^{25}$ D) of −45.7° (in CCl_4).

Authentic Bis(α-phenylethyl) Ether.[18] A mixture of 30 ml of concentrated sulfuric acid, 20 ml of water, and 150 ml of (±)-α-phenylethyl alcohol was stirred for 2 hr at room temperature. The organic layer was washed with water and distilled under reduced pressure. Ether obtained consisted of 45.4% *dl* and 54.6% meso isomer. Since epimerization of bis(α-phenylethyl) ether under the experimental condition was observed to occur very slowly, the composition of authentic ether is kinetically controlled.

2-Octyl α-Phenylethyl Ether. A mixture of 0.1 g-atom of sodium, 20 ml of toluene, and 20 g of 2-octanol was heated under reflux for 5 hr. To this solution 0.1 mol of α-phenylethyl chloride was added and the mixture was heated under reflux for 0.5 hr. The reaction mixture was washed with water and distilled under reduced pressure. 2-Octyl α-phenylethyl ether was separated from this distillate by glc using a 2.0-m poly(ethylene glycol isophthalate), 20% on chromosorb W, column. *Anal.* Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.11; H, 11.52. Two isomers of this ether were separated from the ether mixture using this column.

Isolation of Bis(α-phenylethyl) Ether. A solution of (−)-α-phenylethyl alcohol (1.6 g) in liquid sulfur dioxide (21 ml) was allowed to stand for 3 days and liquid sulfur dioxide was evaporated. From the residual liquid optically inactive bis(α-phenylethyl) ether was obtained using a 0.6-m silicone gum SE-30, 15% on Chromosorb W, column at 140°. *Anal.* Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.67; H, 8.52.

In Scheme I, a 0.6-m silicone gum SE-30, 15% on Chromosorb W, column was used at 140° in procedure a and a 2.0-m poly(ethylene glycol isophthalate), 20% on Chromosorb W, column was used at 160° in procedure b.

General Procedure of Epimerization. Ether and boron trifluoride etherate were sealed in separate glass phials. These phials were set in a reaction vessel, into which solvent was introduced. The reaction was started by breaking the phials. At an appropriate time the reaction was quenched by putting into a dilute alkaline aqueous solution. The product was extracted with ethyl ether and analyzed by glc using a 4.5-m ethylene glycol adipate polyester, 20% on Chromosorb W, column at 180° (for 2-octyl α-phenylethyl ether) or at 200° [for bis(α-phenylethyl) ether].

Registry No.—(−)-α-Phenylethyl alcohol, 1445-91-6; *meso*-bis(α-phenylethyl) ether, 53776-68-4; *dl*-bis(α-phenylethyl) ether, 53776-69-5; 2-octanol, 123-96-6; α-phenylethyl chloride, 672-65-1; *erythro*-2-octyl α-phenylethyl ether, 53716-30-6; *threo*-2-octyl α-phenylethyl ether, 53716-31-7.

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Thermal Decomposition of Some Bis(cyclododecylidene) Cycloalkylidene Triperoxides in Chlorobenzene

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Received September 17, 1974

The effect of substituent and ring size on the rate of decomposition of some bis(cyclododecylidene) cycloalkylidene triperoxides has been studied. Although the effect is not large, there are indications that both the substituent and the ring size may influence the rate of decomposition.

In 1967 Story and coworkers found that the thermal and photochemical decomposition of cyclic di-and triperoxides such as I and II produced macrocyclic hydrocarbons and lactones in fair to good yields.[2] The reaction is represented by eq 1 and 2.

As an extension of this earlier work, we have undertaken a detailed study on the thermal decomposition of peroxides such as I and II. These peroxides have been shown to be important both synthetically and economically.[3] In this paper, as a continuation of our studies on cyclic ketone peroxides, we wish to report our results on the thermal decomposition of the peroxides III and IV.

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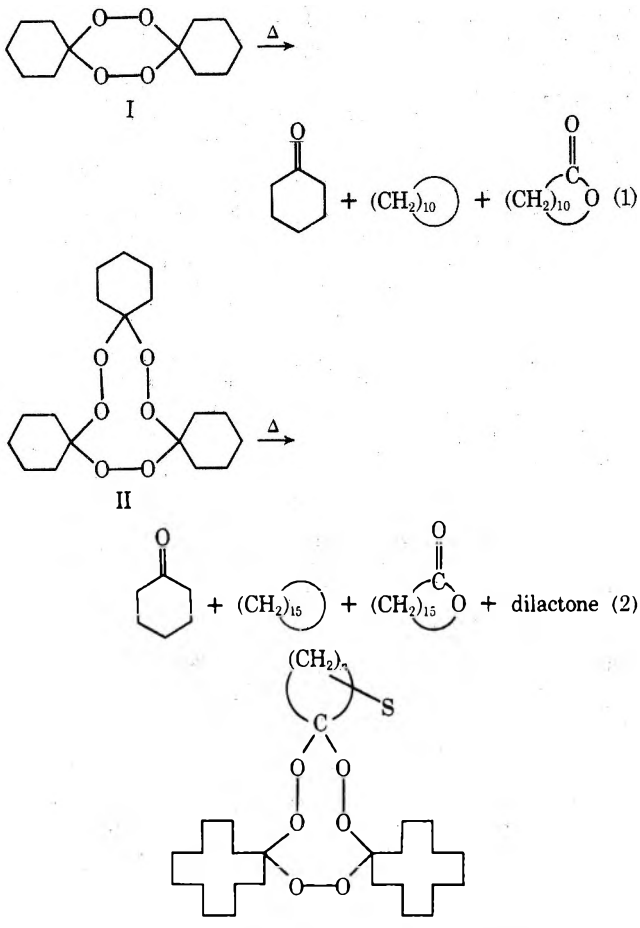
Results

Rate measurements were made on some bis(cyclododecylidene) substituted-cycloalkylidene triperoxides by the spectrophotometric singlet oxygen method previously reported.[4] We have found this method to be useful for following the rate of decomposition of a number of cyclic ketone peroxides. The data are shown in Table I.

For most cyclic ketone peroxides, the rate of decomposition could be monitored at such a low concentration of peroxide that induced decomposition was negligible,[5–7] The solvent chlorobenzene was chosen because it gave the most reproducible results. (Two runs at 155° on IIIa show the reproducibility.)

In order to confirm that this method was actually mea-



III, n = 5: a, S = H; b, S = 4-OMe; c, S = 4-t-Bu; d, S = 4-Et; e, S = 4-Me; f, S = 3-Me; g, S = 2-Me
IV, S = H: a, n = 4; b, n = 6; c, n = 7; d, n = 11

suring the rate of decomposition of the peroxide, several rate measurements were made on IIIa by infrared methods. The run determined at 155° is in excellent agreement with those determined spectrophotometrically. The measurement at 150° falls on the line determined by plotting log k *vs.* $1/T$(°K).

It is interesting to compare the rate of decomposition of this series of peroxides with dicyclohexylidene diperoxide (I) and tricyclohexylidene triperoxide (II). Compound I has a half-life of ~25 min at 160° in chlorobenzene. IIIa has a half-life of ~29 min at 160° in the same solvent. In benzene and toluene, II has a half-life of ~10 min. Thus, it appears that IIIa decomposes at about the same rate as I but at a slightly lower rate than II.

If one examines the other entries in Table I, it is obvious that there is not a large difference in the rate of decomposition although there is a definite trend. The exception is IIIg which decomposes significantly faster than the other entries in Table I.

A semilog plot of rate constant *vs.* σ_m, σ^*, or σ_I[8,9] gives a poor correlation with $\rho \lesssim 0.1$. Thus, the near-zero value of ρ (along with the poor correlation) suggests that inductive effects are not an important factor in the decomposition of this series of peroxides.

Rate measurements were also made on some bis(cyclododecylidene) cycloalkylidene triperoxides IV in chlorobenzene. The data are shown in Table II. Again, it is obvious that the effect of ring size on the rate of decomposition is not large but there is a trend.

This trend is very evident if one examines Figures 1 and 2. Figure 1 is a semilog plot of rate constant *vs.* ring size for some bis(cyclododecylidene) cycloalkylidene triperoxides

Table I
Rate Measurements for Some Bis(cyclododecylidene) Substituted-Cyclohexylidene Triperoxides in Chlorobenzene

Peroxide	T, °C	$10^3 P_0$,[a] M	$10^5 k$, sec^{-1} (±sd)	$t_{1/2}$,[b] min
IIIa	160.1	4.04	40.1 (±2.4)	28.8
	155.1[c]	60.4	30.3	38.0
	155.1	3.82	30.1 (±2.3)	38.3
	155.1	4.04	31.5 (±6.5)	36.7
	150.1[c]	60.0	15.8	73.0
	145.1	4.04	11.4 (±0.6)	101
IIIb	160.1	3.93	35.8 (±3.4)	32.3
	155.1		20.5 (±1.1)	56.5
	150.1		10.5 (±0.9)	110
IIIc	160.1	3.05	41.9 (±2.6)	27.6
	155.1		28.8 (±0.5)	40.1
	150.1		15.3 (±0.6)	75.7
	145.1		6.48 (±0.62)	178
IIId	160.1	2.36	53.5 (±4.3)	21.6
	155.1		27.4 (±1.4)	42.1
	145.1		12.0 (±1.7)	96.6
IIIe	160.1	3.38	47.7 (±2.7)	24.2
	155.1	4.07	27.0 (±0.9)	42.8
	145.1		9.44(±0.69)	122
IIIf	165.1	3.82	63.6 (±3.8)	18.2
	160.1		44.7 (±4.4)	25.8
	150.1		11.0 (±1.1)	105
IIIg	155.1	4.20	91.8 (±3.2)	12.6
	150.1		64.3 (±8.1)	18.0
	145.1		41.0 (±1.5)	28.2
	140.1		34.7 (±2.4)	33.3

[a] Initial peroxide concentration. [b] Half-life. [c] Rate constant obtained by ir methods.

Table II
Rate Measurements for Some Bis(cyclododecylidene) Cycloalkylidene Triperoxides in Chlorobenzene

Peroxide	T, °C	$10^3 P_0$,[a] M	$10^5 k$ sec^{-1} (±sd)	$t_{1/2}$,[b] min
IVa	160.1	3.83	80.6 (±2.5)	14.3
	150.1		32.9 (±1.4)	35.1
	145.1		21.5 (±0.5)	53.8
	140.1	2.78	11.5 (±1.1)	100
IVb	165.1	2.64	56.7 (±7.1)	20.4
	155.1		21.1 (±2.5)	54.7
	150.1		14.8	78.0
IVc	165.1	3.54	77.8 (±8.7)	14.6
	155.1		37.7 (±5.7)	30.6
IVd	165.1	3.54	88.0 (±9.4)	13.1
	160.1		65.2 (±7.8)	17.7
	150.1		30.2 (±4.2)	38.3

[a] Initial peroxide concentration. [b] Half-life.

at 150° in chlorobenzene. The minimum in the curve is around 6 or 7. (The rate constants which determine these two points are the same within experimental error.)

Figure 2 is a semilog plot of rate constant *vs.* ring strain.[10] The plot is typical for a reaction where rate is dependent on ring strain.[11]

Table III contains the activation parameters calculated for nine peroxides. The second, third, and sixth entries of the table contain values which seem to us to be 4–5 kcal high. (This may be due to the fact that values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated from rate constants determined over only 10–15°.)

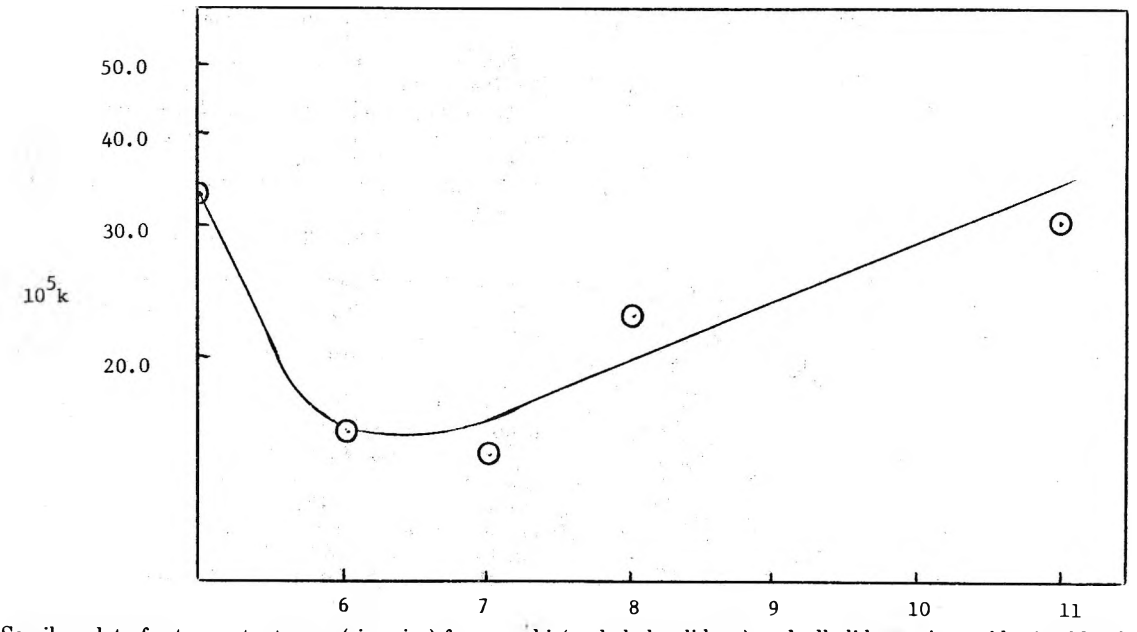


Figure 1. Semilog plot of rate constant *vs.* *n* (ring size) for some bis(cyclododecylidene) cycloalkylidene triperoxides in chlorobenzene at 150°.

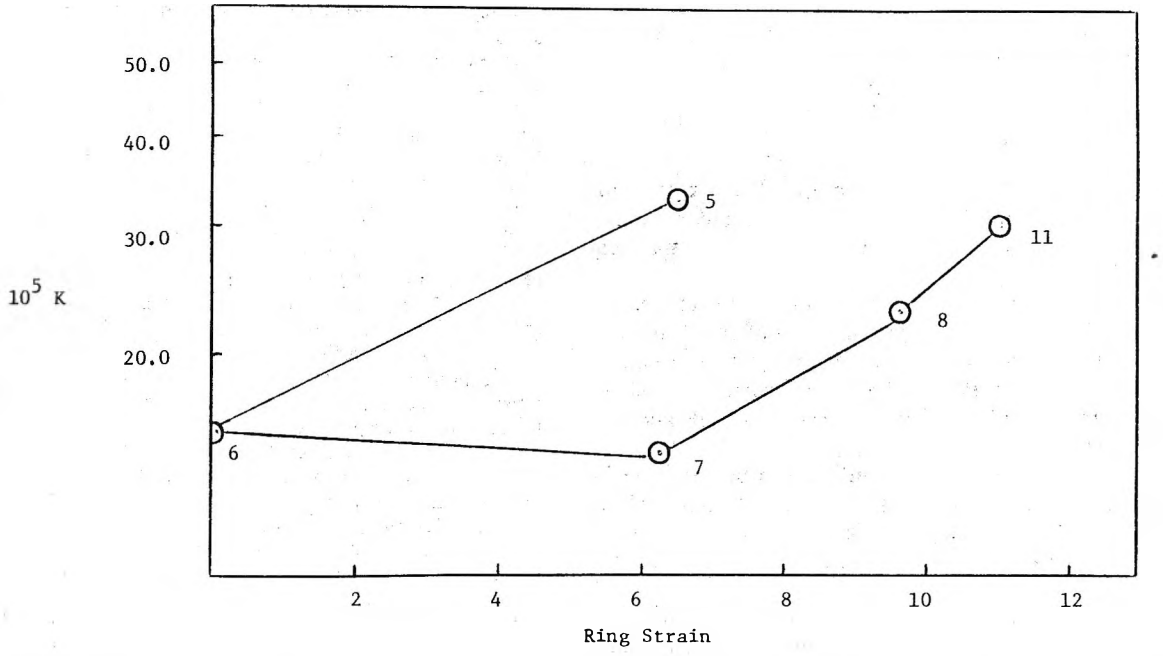


Figure 2. Semilog plot of rate constant *vs.* ring strain for some bis(cyclododecylidene) cycloalkylidene diperoxides in chlorobenzene at 150°.

Table III
Activation Parameters for Some Bis(cyclododecylidene) Cyclohexylidene Triperoxides in Chlorobenzene

Peroxide	$\Delta H^{\ddagger}$, kcal/mol (±sd)	$\Delta S^{\ddagger}$, eu (±sd)	Peroxide	$\Delta H^{\ddagger}$, kcal/mol (±sd)	$\Delta S^{\ddagger}$, eu (±sd)
IIIa	31.1 (±1.1)	1.5 (±2.4)	IIIf	44.1 (±1.7)	30.9 (±3.9)
IIIb	44.4 (±1.1)	31.3 (±2.4)	IIIg	23.8 (±1.7)	−13.8 (±3.8)
IIIc	45.3 (±2.5)	34.1 (±6.0)	IVa	34.0 (±1.0)	9.1 (±2.4)
IIId	34.8 (±1.2)	9.8 (±2.8)	IVb	33.5 (±1.5)	6.3 (±3.5)
IIIe	38.7 (±0.2)	18.7 (±0.5)			

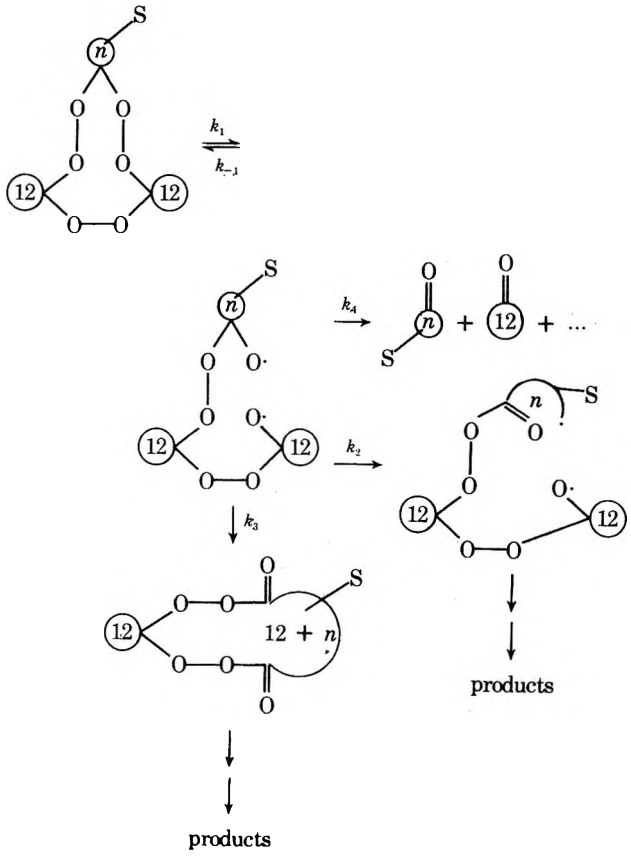
Discussion

The first step in the decomposition of cyclic ketone peroxides is undoubtedly the homolysis of the O–O bond (Scheme I).[12] The above data indicate that this bond is influenced only very slightly (if at all) by inductive effects. Because the diradical formed upon homolysis of one of the O–O bonds cannot diffuse from the solvent cage[13–17] (without rupture of another bond), it probably combines easily to re-form the peroxide.[18]

Once the diradical is formed, it may undergo the other reactions indicated in Scheme I as well as combination to re-form the peroxide. It is in these second steps (k_2, k_3, k_4) where ring size (and therefore ring strain) may influence the rate of decomposition. This may be more apparent if one examines eq 3 which was derived from the data in Scheme I.

$$-\mathrm{d(P)}/\mathrm{d}t = \frac{k_1(k_2 + k_3 + k_4)[\mathrm{P}]}{k_{-1} + k_2 + k_3 + k_4} = k_{\mathrm{obsd}}[\mathrm{P}] \quad (3)$$

Scheme I[18]

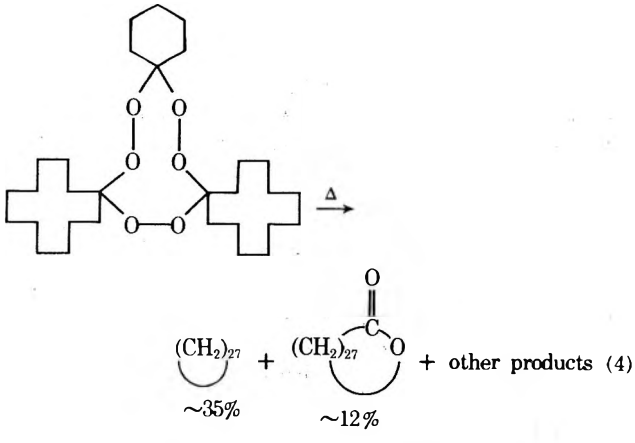


It is also possible for the substituent in III to exert its influence in the second steps (k_2, k_3, k_4) of the decomposition. This may be rationalized in terms of conformational effects.

The effect of alkyl groups on the stability of ring systems has been interpreted by Allinger in terms of the difference in the number of gauche interactions of cyclic and noncyclic analogs.[19] Indeed, it is well-known that alkyl substitution tends to promote cyclization (the so called *gem*-dimethyl effect).[20-23]

Therefore, if alkyl groups may influence the stability of a ring, the rates of the second steps (k_2, k_3, k_4) could well be influenced by the substituent. This would, of course, be reflected in the observed rate of decomposition of the peroxide.

The yields of macrocycles from the thermal decomposition of III and IV have been determined and are entirely typical for a trimeric cyclic peroxide (eq 4). The synthesis



and thermal decomposition of these peroxides for the purpose of macrocyclic synthesis is reported elsewhere.[24]

Experimental Section

Instrumentation. Quantitative ir analysis was done with a Perkin-Elmer IR-621.

A Beckman Model DU uv–visible spectrophotometer was used for the kinetic experiments with tetracyclone.

Two temperature baths were used: (a) a Sargent Model NSI-12 heater and circulator; (b) a Sargent Model NCI-33 heater with a built-in thermostat.

An IBM-360 computer was used for the least-squares treatment of the kinetic data.

Solvents and Reagents. Chlorobenzene (Aldrich) was distilled from a small quantity of tetracyclone and stored in a dark bottle over 4A molecular sieves.

Tetracyclone (Aldrich, mp 218–222°) was used without further purification.

Peroxides. The preparation of peroxides III and IV are given in detail elsewhere.[25]

Preparation of Cuvettes and Vials. Cuvettes were prepared from 10- and 8-mm (inside diameter) Pyrex tubing and were available commercially. A Pyrex glass tube of 5-mm diameter and 80-mm length was fused to the cuvette. A constriction was formed 20 mm from the open end to aid in sealing the cuvette after degassing.

Vials used in the infrared kinetic studies were made in the following manner. An 18 × 150 mm Pyrex test tube was constricted about 20–30 mm from the open end. The test tube was broken at the constriction and a Pyrex glass tube of 5-mm diameter and 80-mm length was fused on. A constriction was formed 20 mm from the open end of the glass tube to be used in sealing off the vial.

Beer's Law for Tetracyclone in Chlorobenzene Solution. Tetracyclone obeyed Beer's law throughout the concentration area of interest.

Infrared Rate Measurements. The procedure has been given in detail.[26]

Spectrophotometric Rate Measurements. Tetracyclone (enough to give 8.00×10^{-4} *M* solution) was weighed out and transferred quantitatively to a volumetric flask. The flask was filled to the mark with solvent and stored in the dark.

Peroxide was then weighed out in a 10- or 50-ml volumetric flask to give the desired concentration. (Ideally enough peroxide was weighed out to cause fading of the tetracyclone to about 0.1 of an absorbance unit.) The volumetric flask containing the peroxide was then filled to the mark with solvent (containing the tetracyclone which had been previously prepared).

The peroxide solution containing tetracyclone was transferred to the prepared cuvette with the aid of a long-stem disposable pipet. The cuvettes were degassed and stored in the icebox until the rate measurements were made.

The vials were placed in the bath at the desired temperature, removed at certain time intervals, quenched in tap water, and rinsed with acetone. The absorbance of tetracyclone monitored at 510 mμ for at least 10 half-lives of the peroxide.

The rate constants reported in the Results and Discussion were obtained by a least-squares treatment of the data thus obtained.

Registry No.—IIIa, 53783-69-0; IIIb, 53783-70-3; IIIc, 53783-71-4; IIId, 53783-72-5; IIIe, 53783-73-6; IIIf, 53783-74-7; IIIg, 53783-75-8; IVa, 53783-76-9; IVb, 53783-77-0; IVc, 53783-78-1; IVd, 53783-79-2.

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Reaction of Polymethylnaphthalenes with Dichlorocarbene. Formation of 1,2:3,4-Bis(dichloromethano)-1,2,3,4-tetrahydronaphthalenes and 1,2-Benzoheptafulvenes

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Received June 13, 1974

Addition of CCl_2 to eight polymethylnaphthalenes which have more than two methyl substituents has been examined. Major products were 1,2:3,4-bis(dichloromethano)-1,2,3,4-tetrahydronaphthalenes (**2**) and 1,2-benzoheptafulvenes (**3**). Benzospirononatrienes (**4** and **5**) were formed only from dimethyl- and 1,4,6,7-tetramethylnaphthalenes. Formation of **2** and **3** was facilitated by increasing the number of methyl substituents and was observed only in the case of naphthalenes which bear at least one 1,4-dimethyl substituent, whereas 3,4-benzoheptafulvenes were detectable only in the form of 3,4-benzospirononatrienes derived from 2,3-dimethyl-substituted rings. The structural determination of **3** is also described.

The preparation of benzoheptafulvene derivatives has been of interest in relation to the chemistry of nonbenzenoid aromatics. A common approach to the synthesis of heptafulvene series seems to start from tropones or benzoheptatrienes.[1] The reaction of methoxynaphthalenes with dichlorocarbene was reported to produce benzotropones.[2] Similarly, the intermediacy of methyl-substituted benzoheptafulvenes was postulated in the reaction of methylnaphthalenes with dichlorocarbene[3] where the isolated products were benzospirononatriene derivatives. However, benzoheptafulvenes were not isolated since they are unstable and undergo further reactions.

In the present paper, we would like to report the preparation of relatively stable polymethyl-substituted benzoheptafulvenes as well as the synthesis of bis(dichloromethano)tetrahydronaphthalenes by the reaction of highly methyl-substituted naphthalenes with dichlorocarbene. In the already reported reaction of octamethylnaphthalene,[4] a 3,4-benzoheptafulvene structure was assigned to one of the dibromocarbene addition products. Our present result, however, indicates that the correct structure must be the 1,2-benzo isomer.

Results and Discussion

An effective synthetic route to polymethylnaphthalenes has been reported[5] and it seems as useful as the long-known procedures involving alkylation and dehydrogenation.[6] Polymethylnaphthalenes which were prepared by the above methods and used in the present study have a C_2 axis of symmetry as to methyl substitution through both nuclei. Dichlorocarbene was generated from chloroform and potassium *tert*-butoxide in a benzene solution of a polymethylnaphthalene at 25°. Reaction products were separated by glpc and column chromatography and their structures were determined mainly by means of spectroscopic analyses. Results are shown in Table I.

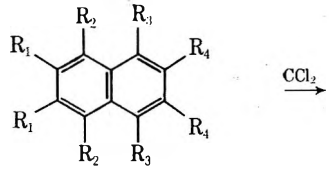
In contrast to the study by Weyerstahl and Blume[3] on mono- and dimethylnaphthalenes where no products such as **2** or **3** were formed but only spirononatriene derivatives **4** or **5** (the same result was obtained in our study only for **1h**), the main products isolated in the reaction of highly methyl-substituted naphthalenes (**1a–g**) were the bis-addition products of CCl_2, *i.e.*, 1,2:3,4-bis(dichloromethano)-1,2,3,4-tetrahydronaphthalenes (**2**), and 4-chloro-1,2-benzoheptafulvenes (**3**). For example, octamethylnaphthalene (**1a**), the highest methyl-substituted homolog of this series, reacted most efficiently with CCl_2 to give **2a** and **3a** in good yields. It is also obvious that the minimum number of methyl substituents required for the formation as well as for the isolation of **2** is two, as indicated by **1g**, and it is four for the formation and isolation of **3**. The yields of both **2** and **3** increased when the number of methyl substituents increased (the total yield almost doubled with two additional methyls).

An increase in the amount of CCl_2 source enhanced the formation of **2** whereas higher temperature favored the formation of **3**; for example, when **1a** was treated with 10 equiv of CCl_2 source at 0°, the yield of **2a** increased to 83%. Since the intermediacy of a 2,3-benzonorcaradiene (**6**) can

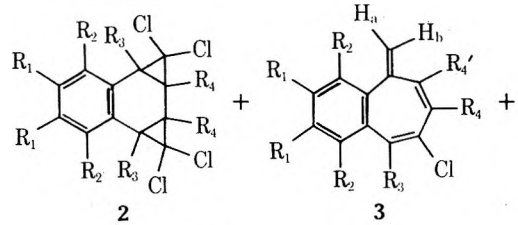
Table I
Reaction of Polymethylnaphthalenes with Dichlorocarbene[a]

Naphthalene (1)	CCl_2/1 mol ratio	Products, % 2	3	4	5	Total yield[e]
OMN (**1a**)	2	30	40			70
OMN (**1a**)	10	83	12			95[b]
1,2,3,4,5,8-HMN (**1b**)	2	16	16			32
1,2,3,4,6,7-HMN (**1c**)	2	17[c]	8			25
1,2,3,4-TMN (**1d**)	2	14	4			18
1,4,5,8-TMN (**1e**)	2	11	4			15
1,4,6,7-TMN (**1f**)	2	3[c]		0.2[c]	6[d]	9.2
1,4-DMN (**1g**)	4	1.5		0.5		2
2,3-DMN (**1h**)	4				5	5

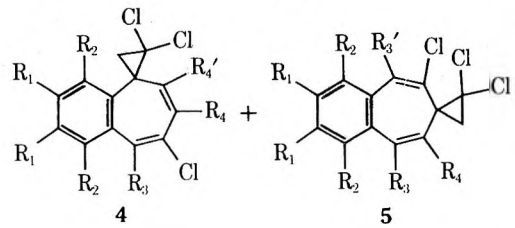
[a] At 25° in benzene. [b] At 0°. [c] CCl_2 added on the 1,4-dimethyl substituted ring. [d] CCl_2 added on the 6,7-dimethyl substituted ring. [e] Recovery of the unreacted naphthalenes was almost quantitative in each case.



1a, $R_1 = R_2 = R_3 = R_4 = Me$
b, $R_1 = H; R_2 = R_3 = R_4 = Me$
c, $R_2 = H; R_1 = R_3 = R_4 = Me$
d, $R_1 = R_2 = H; R_3 = R_4 = Me$
e, $R_1 = R_4 = H; R_2 = R_3 = Me$
f, $R_2 = R_4 = H; R_1 = R_3 = Me$
g, $R_1 = R_2 = R_4 = H; R_3 = Me$
h, $R_1 = R_2 = R_3 = H; R_4 = Me$

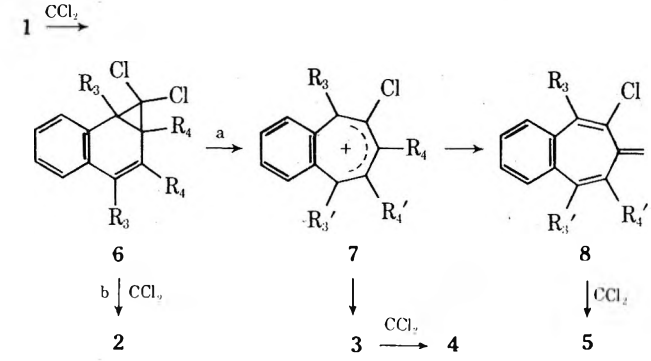


2 **3**



4 **5**

be postulated as the most rational reaction sequence, the two competing reactions (paths a and b in the following scheme) seem easily affected by the temperature, concentration, and substituents. In the reaction of unsubstituted naphthalene with dicyanocarbene generated thermally from the corresponding diazo precursor, the formation of three isomeric benzonorcaradienes was reported.[7] In the present study, however, although the attempt failed to isolate octamethylbenzonorcaradiene intermediates in the reaction of **1a**, a 2,3-benzonorcaradiene must be the only intermediate involved and the other benzo isomers (1,2 and 3,4) are not likely to be formed from CCl_2 generated from chloroform and potassium *tert*-butoxide.



6 **7** **8**

2 **3** **4** **5**

Comparison in the reactivity of the 1,2 bond between 1,4- and 2,3-dimethyl-substituted rings indicates that 2,3-dimethyl substitution enhances the reactivity more than 1,4-dimethyl does[8] as shown in Table I. The total product yield from **1h** (5%) was higher than that from **1g** (2%), for example, and more illustrative was the behavior of **1h**, in which the 5,6 bond was twice as reactive as the 1,2 bond.

That highly methyl-substituted naphthalenes, **1a–e**, formed 1,2-benzoheptafulvenes but not their corresponding spirononatrienes implies that the reactivity of these naphthalenes with CCl_2 is much higher than that of the corresponding 1,2-benzoheptafulvenes. On the other hand, when the number of methyl substituents decreases, the reactivity of naphthalenes decreases and that of benzoheptafulvenes relatively increases to give spirononatrienes as illustrated in cases of **1f–h**.

Another substituent effect is that 1,4-dimethyl substitution seems either to stabilize the first-formed benzonorcaradiene skeleton or to enhance its 4,5-bond reactivity with CCl_2 more noticeably than 2,3-dimethyl substitution does. Thus, in all cases where 1,2-benzoheptafulvenes were isolated, the starting naphthalene necessarily had 1,4-dimethyl substitution and **2** was the main product. In contrast, none of the expected 1:2 adducts was formed from a naphthalene ring having only 2,3-dimethyl substitution (*cf.* **1f** and **1h**). This implies that the first-formed benzonorcaradiene intermediate undergoes ring opening much faster than CCl_2 addition. Most of the reported factors controlling the norcaradiene–cycloheptatriene equilibrium[9] may not be applicable to interpreting the stability of these benzo derivatives, because Cope-type rearrangement, if any, evidently perturbs the aromaticity of the system and therefore an ionic route becomes favorable for the formation of benzotropilium cation, which will be mentioned separately.

The preference of the 1,2-benzoheptafulvene structure to the 3,4-benzo structure was supported by the following nmr analyses. The first evidence was presented by classifying the chemical shift differences between two exo methylene hydrogens in benzoheptafulvene products (see Table II), where two values $\Delta\delta = 0.25$ and 0.05 ppm were obtained, each corresponding to the structure with and without α-methyl groups on the unaffected benzene ring, respectively. In a 1,2-benzoheptafulvene structure, the expected peri interaction[10] between one of the exo methylene protons and α-methyl on the benzene ring increases the difference in chemical shifts between two methylene protons, whereas such an effect will not be significant in any 3,4-benzo structure (a similar effect is also shown in benzospirononatrienes, see Table III). The second nmr evidence is presented by the comparison of the chemical shifts of two α substituents (CH_3 or H) on the unaffected benzene ring with those of benzospirononatriene products (**4** and **5**) whose structures have been unequivocally established[3] (compare Tables II and III). Since the chemical shifts of two α hydrogens on the benzene ring of **4** appeared unequivalent whereas those of **5** appeared equivalent, we can presume to say that a closer location of the spiro moiety to the benzene ring will increase the chemical shift differences between two α substituents and also between two cyclopropane methylene hydrogens. With the same logic, the observed unequivalency in the chemical shifts of two R_2 groups in any of the isolated heptafulvenes leads us to support the 1,2-benzo structure.

A mechanistic consideration also gives a preference not only to the 1,2-benzo structure but also to the structure **10** over the alternative structure **12**. Among the three possible canonical structures **9a–c** of benzotropilium cation **7** which is formed by the solvolytic rearrangement of **6**, **9a** seems to have the lowest energy due to its benzylic character and the location of the electronegative chlorine atom substituted far from the cationic center, whereas both **9b** and **9c** have their chlorine on a vinyl position vicinal to the positive charge and the former may have a more or less nonplanar conjugation. Since any nucleophilic displacement by *tert*-butoxide or chloride anion is unlikely in this equilibrium, then, when $R_3 = R_3' =$ methyl, proton elimination from R_3' takes place to form 1,2-benzoheptafulvene (**10**). On the

Table II
Nmr Spectra of Methyl-Substituted 4-Chloro-1,2-benzoheptafulvenes (3)

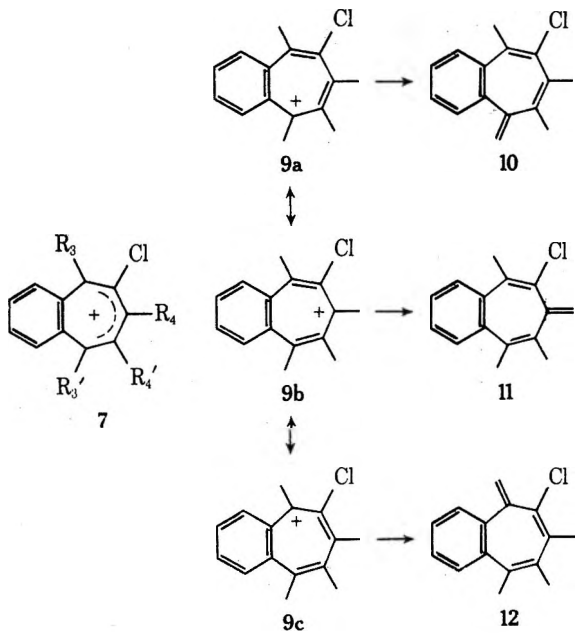
Compd no.	Starting naphthalene	Chemical Shifts, τ						Δδ(CH_2) ppm
		R_1	R_2	R_3	R_4	R_4'	*exo*-CH_2	
3a	**1a**	Me 7.83	Me 7.83 7.90	Me 7.73	Me 8.22	Me 8.08	4.86 5.15 J = 2.0	0.29
3b	1b	H 3.00[a] 3.08	Me 7.69 7.71	Me 7.83	Me 8.18	Me 8.02	4.80 5.03 J = 2.0	0.23
3c	**1c**	Me 7.76	H 2.92 3.22	Me 7.68	Me 8.17	Me 8.02	4.97 5.02 J = 2	0.05
3d	**1d**	H 2.75–H 3.05[b]		Me 7.67	Me 8.14	Me 8.02	4.96 5.01 J = 2	0.05
3e	1e	H 2.99 3.08	Me 7.69 7.71	Me 7.77	H 4.10	H 3.64	4.76 4.97 J = 1.7	0.21
13	1a	Me 7.83	Me 7.83 7.90	Me 7.73	Me 8.20	Me 8.10	4.85 5.14 J = 2.0	0.29
16[c]	1a	Me 7.71,7.79, 7.80,7.82		Me 7.95	Me 8.34	Me 8.08	4.97 5.25 J = 2.2	0.28

[a] AB type, J = 8 Hz. [b] Multiplet. [c] Vinylic H which replaced Cl in **3a** appeared at 4.01.

Table III
Nmr Spectra of Benzospirononatrienes (4 and 5)

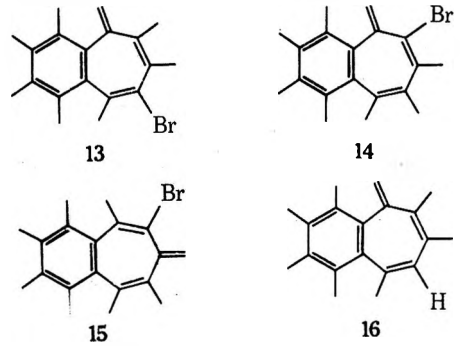
Compd no.	Chemical Shifts, τ							Δδ(CH_2), ppm
	R_1	R_2	R_3	R_3'	R_4	R_4'	*exo*-CH_2[a]	
4f	Me 7.71 Me 7.73	H 2.73 H 3.14	Me 7.53[c]		H 3.80[c] (J = 9)	H 4.45 (J = 9)	7.75 8.13	0.38
4g	H 2.35–H 2.90[b]		Me 7.51		H 3.72 (J = 10)	H 4.40 (J = 10)	7.75 8.07	0.32
5f	H 3.06	Me 7.63	H 3.32 (J = 1.5)	H 3.03		Me 7.79 (J = 1.5)	8.00 8.14	0.14
5h	H 2.74	H 2.74	H 3.20 (J = 1.5)	H 2.93		Me 8.04 (J = 1.5)	7.90 8.10	0.20

[a] AB type, J = 7.5–8.0 Hz. [b] Multiplet. [c] J = 0.5 Hz.



other hand, when R_3 = R_3' = hydrogen but R_4 = methyl, proton elimination from R_4 in the less favorable cation **9b** takes place to terminate the life of the cation. Therefore, from naphthalenes **1a–d** bearing four methyls on one ring, the formation of 1,2-benzoheptafulvenes is more favored, at least kinetically, than those of **12** and 3,4-benzo alternatives **11**.

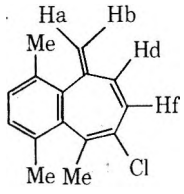
Different from the above consideration, a 3,4-benzo structure **15** was postulated tentatively for a bromobenzo-



heptafulvene product obtained in the reaction of **1a** with CBr_2.[4,11] Though on reexamination we obtained the same reaction product as reported, its nmr spectrum was almost identical with the corresponding chloro derivative (*cf.* **13** and **3a** in Table II) and, moreover, the reduction of both **13** and **3a** with 2 equiv sodium naphthalene in THF at −50° gave the identical products[12] which were assigned the structure **16** on the basis of spectral evidence; therefore, the reported structure **15** should be replaced by **13**. The reduction product showed four aromatic methyls as singlets at τ 7.71, 7.79, 7.80, and 7.82, a doublet at 7.95 (3 H, J = 1.4 Hz coupling with a vinylic H, m, at 4.01), two broad singlets at 8.08 and 8.34 (allylic methyls coupling with each other by J = 0.5 Hz, and the latter also coupling slightly with H at 4.01), and a pair of doublets at 4.97 and 5.25 (exo methy-

lene, J = 2.15 Hz). In this spectrum, three observations were made to assign the structure to 3,5,6-trimethyl-1,2(tetramethylbenzo)heptafulvene (**16**) rather than the 3,4,5-trimethyl isomer: (a) no coupling was observed between either of the exo methylene hydrogens and the vinylic hydrogen at 4.01, while in **3e** a coupling between each of the methylene hydrogens and the vinylic hydrogen (probably at the 6 position) was observed (J = 1.8 Hz, see the following paragraph); (b) the vinylic H at 4.01 couples with a methyl at 7.95 (J = 1.4 Hz) which appears at the lowest field among three allylic methyls; (c) the displacement of Cl by H does not influence the chemical shift difference between two exo methylene hydrogens in **3a** (see $\Delta\delta$ in Table II).

Additional support of the structure **10** may be presented by inspecting the spin–spin coupling mode in the product **3e**. The observed spectrum of this compound showed a triplet for one of the methylene hydrogens, and the J value between two endo vinylic hydrogens was as large as 10.2 Hz. Referring to the spectrum calculated for *trans*-1,3-butadiene,[13] the compound was assigned the structure **3e** having the chlorine atom at the 4 position.



3e

$J_{ab} = 1.8$
$J_{ad} = 1.8$
$J_{af} = 0.8$
$J_{bd} = 1.8$
$J_{df} = 10.2$

1,2-Benzoheptafulvenes, thus obtained in the present study, are not so stable except **3a** and darken on standing at room temperatures; on the other hand, 1,2:3,4-bis(dichloromethano)-1,2,3,4-tetrahydronaphthalenes (**2**), whose nmr spectra are tabulated in Table IV, are quite stable. And some novel reactions[14] of this geometrically strained system are now under way.

Table IV
Nmr Spectra of 1,2:3,4-Bis(dichloromethano)-1,2,3,4-tetrahydronaphthalenes (2)

Compd no.	Chemical Shifts,[a] τ R_1	R_2	R_3	R_4
2a	Me 7.79	Me 7.72	Me 8.41	Me 8.69
2b	H 3.07	Me 7.68	Me 8.45	Me 8.68[b]
2c	Me 7.78	H 2.88	Me 8.43	Me 8.52
2d	H 2.80	H 2.60	Me 8.39	Me 8.46[c]
2e	H 3.06	Me 7.62	Me 8.50	H 8.13
2f	Me 7.76	H 2.87	Me 8.35	H 7.97
2g	H 2.75	H 2.65	Me 8.32	H 7.90[b, c]

[a] In CCl_4, singlet unless otherwise stated. [b] In $CDCl_3$, 60 MHz. [c] R_1 and R_2 showed an A_2B_2 pattern.

Experimental Section

Nmr spectra were recorded on Jeol 4H-100 and Varian HA-100 spectrometers (100 MHz) and chemical shifts are given in τ units. These data are tabulated in Tables II, III, and IV. Ultraviolet spectra were taken on a Hitachi 124 model. Melting points are uncorrected. Combustion analysis was performed by the Microanalytical Laboratory of Kyoto Univeristy.

Synthesis of Polymethylnaphthalenes. Four polymethylnaphthalenes, **1a–d**, were prepared according to the procedure reported.[4] Three naphthalenes, **1e–g**, were prepared by Mosby's method.[6] 2,3-Dimethylnaphthalene (**1h**) was commercially available.

Reaction of Polymethylnaphthalenes with Dichlorocarbene. To a stirred mixture of a polymethylnaphthalene (0.01 mol) and potassium *tert*-butoxide (0.02 mol) in 60 ml of dry benzene was added chloroform (0.02 mol) over a period of 30 min at 25°. After additional stirring at 25° for 4 hr, the reaction mixture was quenched by adding 20 ml of water. The organic layer was separated, the aqueous layer was extracted two times with 20 ml of benzene, and organic phases were combined, washed with water, and dried over anhydrous magnesium sulfate. A small portion of the benzene solution was analyzed by glpc (SE-30, 3%, 1 m) in which the eluting order of the reaction products was **3**, **1**, **4** or **5**, and **2**. The remainder of the solution was evaporated *in vacuo* to dryness and the product mixture was submitted to the separation procedures mentioned below for each reaction. In the following descriptions, column-chromatographic separations were carried out with silica gel using cyclohexane as eluent, and preparative glpc separations were carried out with a SE-30 column (3%, 1 m).

Octamethylnaphthalene (1a). The product mixture was chromatographed first to remove the unreacted **1a** and the obtained mixture of **2a** and **3a** was recrystallized from cyclohexane to give needle-like crystals of **2a**: mp 250–251°; $P^+(m/e)$ 404; uv (cyclohexane) 223 nm (ϵ 35,300), 288 (302), and 297 (223).

Anal. Calcd for $C_{20}H_{24}Cl_4$: C, 59.13; H, 5.97. Found: C, 58.89; H, 5.98.

After removing **2a** as much as possible, the remainder was recrystallized from ethanol to give pure **3a** as block crystals: mp 125–126°; $P^+(m/e)$ 286.

Anal. Calcd for $C_{19}H_{23}Cl$: C, 79.56; H, 8.08. Found: C, 79.30; H, 8.11.

1,2,3,4,5,8-Hexamethylnaphthalene (1b). The product mixture was separated into a mixture of **2b** and **3b** and unreacted **1b** by a column chromatography, in which the former eluted first. From the mixture of **2b** and **3b**, **2b** was isolated as colorless crystals by recrystallization from cyclohexane: mp 169.5–170.5°; $P^+(m/e)$ 376.

Anal. Calcd for $C_{18}H_{20}Cl_4$: C, 57.16; H, 5.34. Found: C, 56.86; H, 5.28.

A preparative glpc of the cyclohexane filtrate gave **3b**: liquid; P^+ (m/e) 258; uv (cyclohexane) 225 nm (20,400), 260 (9080).

Anal. Calcd for $C_{17}H_{19}Cl$: C, 78.91; H, 7.41. Found: C, 78.62; H, 7.70.

1,2,3,4,6,7-Hexamethylnaphthalene (1c). Recrystallization of the product mixture from cyclohexane recovered a part of unreacted **1c**, and the filtrate was column chromatographed into two fractions. The first fraction consisted of **2c** and **3c**, and the second fraction of unreacted **1c**. Recrystallization of the first fraction from benzene afforded colorless solids of **2c**: mp 177.5–178°.

Anal. Calcd for $C_{18}H_{20}Cl_4$: C, 57.16; H, 5.34. Found: C, 56.99; H, 5.28.

A preparative glpc of the benzene filtrate gave **3c**: liquid; $P^+(m/e)$ 258; uv (cyclohexane) 232 nm (23,200), 271 (9160).

Anal. Calcd for $C_{17}H_{19}Cl$: C, 78.91; H, 7.41. Found: C, 78.08; H, 7.75.

1,2,3,4-Tetramethylnaphthalene (1d). The procedure of the product separation was similar to that mentioned above for **1c**, except petroleum ether was used as a recrystallization solvent. **2d**: mp 113–114°.

Anal. Calcd for $C_{16}H_{16}Cl_4$: C, 54.88; H, 4.61. Found: C, 54.68; H, 4.87.

3d: liquid; $P^+(m/e)$ 230; uv (cyclohexane) 225 nm (21,000), 263 (7000).

Anal. Calcd for $C_{15}H_{15}Cl$: C, 78.08; H, 6.55. Found: C, 77.81; H, 6.76.

1,4,5,8-Tetramethylnaphthalene (1e). Recrystallization of the product mixture from petroleum ether afforded a solid which consisted of **2e** and **1e**. This mixture was chromatographed to give pure **2e**: mp 171–171.5°.

Anal. Calcd for $C_{16}H_{16}Cl_4$: C, 54.88; H, 4.61. Found: C, 55.07; H, 4.64.

The petroleum ether filtrate was also chromatographed to give **3e** containing a small amount of **2e** which could be removed by a preparative glpc. **3e**: liquid; $P^+(m/e)$ 230; uv (cyclohexane) 260 nm (9000).

Anal. Calcd for $C_{15}H_{15}Cl$: C, 78.08; H, 6.55. Found: C, 77.84; H, 6.79.

1,4,6,7-Tetramethylnaphthalene (1f). The product mixture was distilled using a saber-shaped flask to remove unreacted **1f**. The residual material was separated into three fractions by a column chromatography. The first fraction consisted of **2f** and **5f**, the second fraction consisted of **1f**, and the last consisted of **4f**. **4f:** mp 187–188.5°; $P^+(m/e)$ 312; uv (cyclohexane) 219 nm (26,200), 274 (7920).

Anal. Calcd for $C_{16}H_{15}Cl_3$: C, 61.27; H, 4.82. Found: C, 61.15; H, 4.82.

Recrystallization of the first fraction from benzene afforded colorless crystals of **2f:** mp 217.5–218.5°.

Anal. Calcd for $C_{16}H_{16}Cl_4$: C, 54.88; H, 4.61. Found: C, 55.15; H, 4.43.

Pure **5f** was obtained from the filtrate by changing the recrystallization solvent to methanol: mp 92–93.5°; $P^+(m/e)$ 312; uv (cyclohexane) 239 nm (32,100), 310 (1020).

Anal. Calcd for $C_{16}H_{15}Cl_3$: C, 61.27; H, 4.82. Found: C, 61.00; H, 5.07.

1,4-Dimethylnaphthalene (1g). The product mixture was distilled *in vacuo* to remove unreacted **1g**. The residual material was chromatographed into three fractions. The first fraction consisted of **2g** and **1g**, the second fraction consisted of **1g**, and the last consisted of **4g**. **4g:** liquid; $P^+(m/e)$ 284; uv (cyclohexane) 228 nm (16,000), 272 (6310).

Anal. Calcd for $C_{14}H_{11}Cl_3$: C, 58.88; H, 3.88. Found: C, 59.28; H, 4.26.

Pure **2g** was obtained by a preparative glpc separation of the first fraction: mp 155–156°.

Anal. Calcd for $C_{14}H_{12}Cl_4$: C, 52.21; H, 3.76. Found: C, 52.50; H, 3.97.

2,3-Dimethylnaphthalene (1h). The product mixture was recrystallized from cyclohexane to remove the unreacted **1h**. The filtrate was chromatographed by preparative glpc to give **5h:** mp 93.5–95.5°; $P^+(m/e)$ 284; uv (cyclohexane) 240 nm (40,680), 263 (5770).

Anal. Calcd for $C_{14}H_{11}Cl_3$: C, 58.88; H, 3.88. Found: C, 58.98; H, 3.81.

Reduction of 3a (as well as of 13) with Sodium Naphthalene. 4-Chloro-3,5,6-trimethyl-1,2-(tetramethylbenzo)heptafulvene (**3a**, 1.0 g, 3.5 mmol) was dissolved in dry THF (50 ml), and the solution was flushed with purified nitrogen stream for 20 min. To this solution at −50° was added dropwise 8 ml (*ca.* 7 mmol) of a THF solution of sodium naphthalene prepared from 2.3 g of sodium metal and 12.8 g of naphthalene in 100 ml of THF. After an additional 1 hr of stirring at −50°, 10 ml of a mixture of THF and water (3:1) was added to the reaction flask and the temperature was raised to 25°. Water (50 ml) was added, the reaction mixture was extracted with ether, and the ethereal solution was dried over anhydrous magnesium sulfate. After evaporating solvent, naphthalene was removed by sublimation at 40° (2 mm). The glpc analysis of the residue proved that **16** was the only product detectable and the remainder was chromatographed by silica gel and petroleum ether to give 3,5,6-trimethyl-1,2-(tetramethylbenzo)heptafulvene (**16**): 0.20 g (23%); mp 104.5–105°; $P^+(m/e)$ 252. For the nmr spectrum, see the text.

Reduction of **13** with sodium naphthalene by the same procedure gave the identical product with **16** in a 48% yield.

Registry No.—**1a**, 18623-61-5; **1b**, 36230-30-5; **1c**, 17384-76-8; **1d**, 3031-15-0; **1e**, 2717-39-7; **1f**, 13764-18-6; **1g**, 571-58-4; **1h**, 581-40-8; **2a**, 52033-53-1; **2b**, 53849-11-9; **2c**, 53849-12-0; **2d**, 53849-13-1; **2e**, 53849-14-2; **2f**, 53849-15-3; **2g**, 53849-16-4; **3a**, 53849-17-5; **3b**, 53849-18-6; **3c**, 53849-19-7; **3d**, 53849-20-0; **3e**, 53849-21-1; **4f**, 53849-22-2; **4g**, 53849-23-3; **5f**, 53849-24-4; **5h**, 29042-89-5; **13**, 53849-25-5; **16**, 53849-26-6; dichlorocarbene, 1605-72-7.

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(10) Review: V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).
(11) When the reaction of **1a** with CBr_2 was carried out at higher temperatures than 30°, another product to which we tentatively assign the structure **14** was obtained in a low yield. The nmr spectrum of this product showed its exo methylene protons at 4.64 and 5.05 as a pair of doublets.
(12) When some excess amount of sodium naphthalene was used in this reduction, the exo double bond of **13** was reduced to give a mixture of two isomeric benzocycloheptatrienes.
(13) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N.Y., 1969, p 342.
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Protonation in Superacid Solution of Selected Exo-Methylene Polyunsaturated Alicyclics. Monomethyl 1,3-Bishomotropylium, Bicyclo[3.2.2]nonatrienyl, and Norbornadienyl Cations[1]

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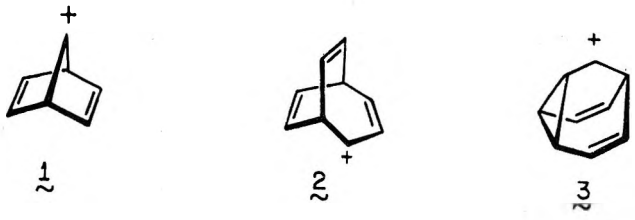
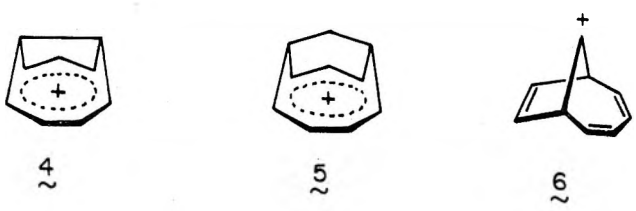
Received August 27, 1974

^{1}H NMR and ^{13}C NMR spectral studies of the protonation of 9-methylenebarbaralane (**7**), 5-methylenetricyclo[6.1.0.0^{4,9}]nona-2,6-diene (**8**), 9-methylenebicyclo[4.2.1]nona-2,4,7-triene (**9**), 2-methylenebicyclo[3.2.2]nona-3,6,8-triene (**13**), 7-methylenequadricyclane (**18**), and 7-methylenenorbornadiene (**19**) in FSO_3H–SO_2ClF are reported. In the first three examples (isomeric $C_{10}H_{10}$ hydrocarbons), exposure to superacid at −135° gave exclusively the bishomoaromatic 1-methylbicyclo[4.3.0]nonatrienyl cation (**10**). In contrast, analogous treatment of **13** (a fourth $C_{10}H_{10}$) at −80° led cleanly to the stable 2-methylbicyclo[3.2.2]nonatrienyl cation (**14**), the first example of this heretofore elusive system. The stability and spectral features of **14** signify no obvious antibicycloaromatic character or other destabilization. With **18** and **19**, direct conversion to the 7-methylnorbornadienyl cation was observed. Spectral data concerning the ground-state polarization of the exo-methylene polyolefins are also presented and discussed.

Current interest in the electronic requirements for longicyclic stabilization[3] has prompted generation of several bi- and tricyclic carbocations under solvolytic conditions or in superacid solvents. The most intensely studied member of this group, the 7-norbornadienyl cation (**1**), is widely recognized to be highly stabilized.[4] Its distorted nature provides supportive evidence for the claim that homoaromatic interaction[5] is the major contributing factor to its "bicycloaromatic" character.[6] Various attempts to generate the bicyclo[3.2.2]nona-2,6,8-trienyl cation (**2**) have resulted instead in exclusive formation of the 9-barbaralyl cation (**3**).[6,7] The



initial claim that this facile rearrangement arises because of inherent "antibicycloaromatic" destabilization in **2**[7a] has been refuted in favor of its access to a low-energy route leading to energetically favored **3**.[7d] The bicyclo[4.3.0]nonatrienyl (**4**) and bicyclo[4.3.1]deca-2,4,7-trienyl cations (**5**) enjoy charge delocalization of the bishomotropylium type.[7g,8] In fact, **4** is the ion to which **3** rearranges at temperatures of −125° and above.[7e] The bicyclo[4.2.1]nona-2,4,7-trienyl cation (**6**) is likewise very prone to skeletal

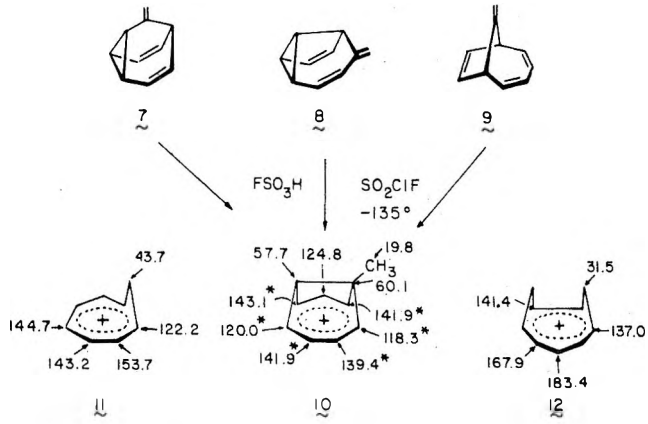


isomerization with formation of dihydroindenyl cations,[9] despite its predicted "bicycloaromatic" nature.[3,10]

In recently published work,[11] one of our groups demonstrated that electrophilic addition to exocyclic methylene precursors of such cationic intermediates was a serviceable probe of possible longicyclic interactions. We have now investigated the protonation of several such alicyclic polyolefins under long-life conditions and wish to report the direct observation of the methyl-substituted carbocations. With but one exception, the 9-methyl-9-barbaralyl cation,[7g,12] no substituted derivatives of these ions have previously been investigated.

Results and Discussion

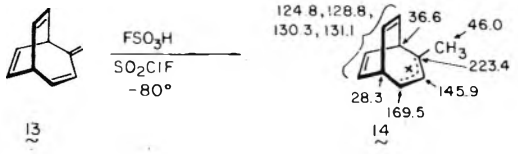
Protonation of $C_{10}H_{10}$ Isomers. When protonated in FSO_3H–SO_2ClF at −135°, hydrocarbons **7**,[11,13,14] **8**,[11,14] and **9**[9b,11,15] underwent ready conversion to the 1-methylbicyclo[4.3.0]nonatrienyl cation (**10**), the ^{1}H NMR spectral



properties of which were identical with those previously reported by Winstein.[7g] The ^{13}C NMR spectrum of **10** was obtained at −90° using the Fourier transform technique and the carbon shifts (in parts per million relative to capillary TMS)[16] are shown alongside the structure. For comparison purposes, carbon shifts are also given for the mono- (**11**) and 1,3-bishomotropylium ions (**12**), recorded under similar conditions.[17] Of the seven "basal" carbons in **10**, four appear at rather low field (139–143 ppm) and the remaining three in more shielded environments (118–125 ppm). These shifts reveal that extensive charge delocalization is present in **10** such that the bishomoaromatic formalism suitably represents its electronic structure. However, even after account is taken of the rehybridization necessary for homointeraction, it is seen that the pair of methine bridges serve to reduce the level of delocalization as com-

pared to **11**. In the latter case, the ring carbon shifts, exclusive of those due to C_1 and C_7, are more equally deshielded in accord with more equitable dispersal of the positive charge. The cyclic delocalization in **10** remains, however, at a higher level than in **12**, where the range of relevant carbon shifts is now greater than 40 ppm. That this ion possesses a ring current of lessened magnitude than that in **10** is also suggested by HMO calculations, which deduce that only 0.24 unit of positive charge is provided to the ethylenic moiety in **12** compared to 0.50 unit of positive charge donated away from the allylic part of **10** into its butadiene unit.[7g]

Treatment of 2-methylenebicyclo[3.2.2]nona-3,6,8-triene (**13**)[11,14] with FSO_3H–SO_2ClF at −135° gave a dark brown solution which was stable at −80° for days. ^1H NMR and ^{13}C NMR spectral analysis of this solution signaled the formation of **14**, the first example of the heretofore elusive[6,7] bicyclo[3.2.2]nonatrienyl class of cations. The charge

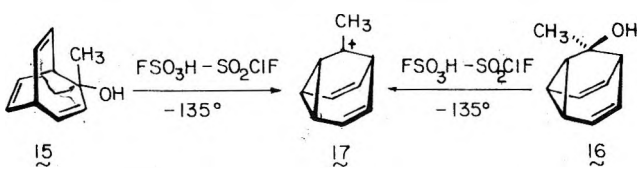


13 14

distribution in **14**, as reflected by the chemical shifts of the peripheral protons and ring carbon atoms, is totally unlike that in **10** and **12** and as such can only be viewed as a *simple allylic ion*. Reference ions having allylic part structures have previously been described.[18] Of particular significance, the four olefinic protons on the two etheno bridges show normal olefinic character (Figure 1), as do the attendant carbon atoms. Consequently, the spectroscopic properties of **14** are uniquely concordant with the absence of interaction between the allylic cation moiety and the double bonds.

Furthermore, there is no evidence of inherent instability or unusual destabilization. Within narrow limits **14** gives every indication of being comparable to other allylic cations, notwithstanding the adverse inductive effect of the two additional double bonds. Cyclic charge delocalization involving one etheno bridge would make five of the carbon atoms carry a substantial part of the cationic character. However, this species would be electronically destabilized relative to the allylic moiety owing to its bishomocyclopentadienyl cation nature; as a result, it gains no importance. For similar reasons, antibicycloaromatic character is seen not to develop.

The observation that **7** and **13** do *not* undergo protonation to give the same cation contrasts significantly with the earlier finding that tertiary alcohols **15** and **16** are both ionized directly to the 9-methyl-9-barbaralyl ion (**17**) at −135°



15 17 16

under otherwise comparable conditions.[7g,12] Rather, proton transfer to **13**, occurring as it does uniquely at the exomethylene group, does not trigger homoallylic participation which would lead directly to **17**. Is methyl substitution at C_2 of the bicyclo[3.2.2]nonatrienyl cation as in **14** adequate to endow this cation with greater thermodynamic stability than its barbaralyl counterpart? This question is difficult to answer given only the present data. It would seem, however, that the direct conversion of **15** to **17** with resultant

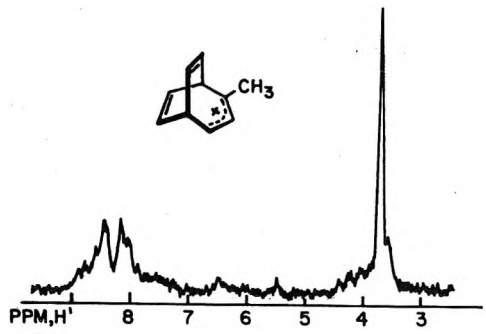
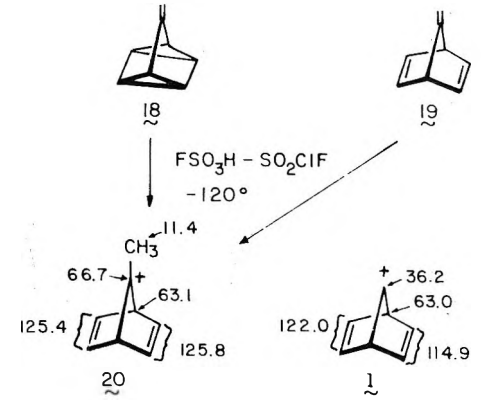


Figure 1. ^1H NMR spectrum (60 MHz) of the 2-methylbicyclo[3.2.0]nonatrienyl cation (**14**). The six olefinic protons appear downfield while the two bridgehead protons and the methyl group are seen at high field.

bypass of ion **14** arises by virtue of anchimeric assistance to C–O bond cleavage in the protonated alcohol. Since bond breaking is not involved in protonation reactions of exomethylene compounds, energy requirements for cation formation are phenomenologically lessened and neighboring group participation is unnecessary. In principle therefore, protonation studies of exo-methylene derivatives are to be preferred to those involving tertiary methyl-substituted alcohols.

Methylenequadricyclane and Methylenenorbornadiene in Superacid. When **18**[11,19] and **19**[11,19] were carefully added to FSO_3H–SO_2ClF solutions at both −120 and −78°, solutions of the 7-methylnorbornadienyl cation (**20**) were formed. The ^1H NMR spectrum is as expected for this

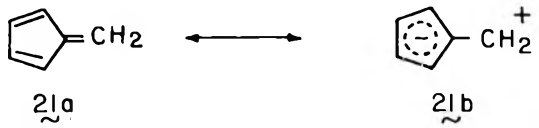


20 1

species,[20] showing a methyl singlet at δ 1.86 and multiplets for the bridgehead, olefinic, and homoaromatic protons at δ 5.18, 6.32, and 7.70, respectively. ^{13}C NMR data for the parent norbornadienyl cation have previously been reported (see **1**).[21] The ^{13}C NMR parameters evidenced by **20** compare favorably and point up an interesting additional feature. The presence of the methyl group at C_7 serves to make the signals due to C_2 and C_3 almost identical in their chemical shift with those of C_5 and C_6. This probably arises from the expectedly[22] lessened electronic demand at C_7, which in turn diminishes the need for homoaromatic stabilization and lessens conformational distortion.

Ground-State Polarization of the Exo-Methylene Hydrocarbons. To infer longicyclic interaction in the neutral exo-methylene compounds would require that polarization of the exocyclic double bond operate in a direction which would electronically stabilize the particular molecule. In more classical systems such as fulvene (**21**) and heptafulvene (**22**), their differing reactivity characteristics have been ascribed to the existence of appreciable dipolar character which places opposite charge on the respective methylene groups. Access to cyclopentadienide and tropy-

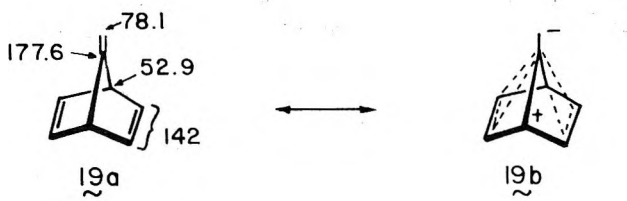
lium ion character underlies the otherwise energetically unrewarding charge separation.



21a 21b

22a 22b

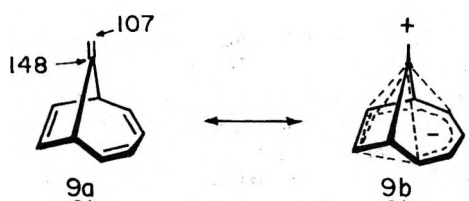
The excessive shielding of the methylene carbon in 7-methylenenorbornadiene (**19**) relative to 7-methylenequadricyclane (**18**) and 7-methylenenorbornane (**23**) has previously been commented upon.[11,19] The appearance of the methylene proton signal in **19** (δ 3.63) approximately 0.9 ppm to higher field than those in **18** and **23** is believed to point up the strong shielding arising from polarization which orients the negative terminus of the dipole away from the bicyclic framework. That structure **19b** contributes significantly to the ground state is suggested further by its dipole moment (0.71 D) and ^{13}C NMR parameters.[19] In particular, the magnitude of $\Delta\delta$ (>C=CH_2) for **19** (99.5 ppm) is enormously larger than those for **18** (56.2 ppm) and **23** (61 ppm).



19a 19b

18 23

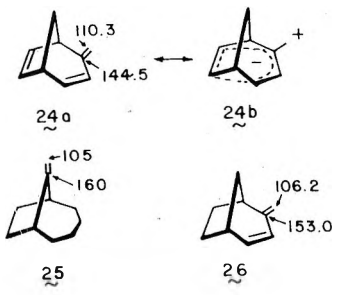
The ^{13}C NMR spectrum of **9**[15] was seen to exhibit a chemical shift difference for the methylene group of 41 ppm, a value far smaller than that for **19** and actually distinctly less than the average $\Delta\delta$ value of approximately 50–60 ppm seen for nonpolarized cyclic methylene compounds such as **23** and **25**. This can be accounted for in terms of contributions from zwitterion **9b**, an interpreta-



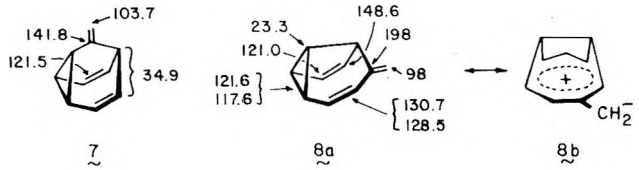
9a 9b

tion which compares favorably with that offered in explanation of the ^{13}C NMR data for 2-methylenebicyclo[3.2.1]-octa-3,6-diene (**24**, $\Delta\delta$ = 34.2 ppm, μ = 0.59 D).[23] By way of comparison, **26** exhibits a quite normal $\Delta\delta$ value of 47.8 ppm.[23b]

Judging from the ^{13}C NMR spectrum of 9-methylenebarbaralane (**7**), where a $\Delta\delta$ of 38.1 is seen, it would appear that the exocyclic double bond is in this instance also giving up a small portion of its charge density to the remainder of the π system.



24a 24b 25 26



7 8a 8b

On this basis, the large $\Delta\delta$ for **8** (100 ppm) would appear to be a direct consequence of an inherent tendency for development of ground-state 1,4-bishomotropylium ion character. Interestingly, the substitution pattern in **8b** is not the same as that which is ultimately realized upon protonation.

Experimental Section

Materials. The preparation of the hydrocarbons has been previously described.

Proton Nuclear Magnetic Resonance Spectroscopy. ^1H NMR spectra were obtained using Varian Associates Model A56/60A and HA 100 NMR spectrometers equipped with variable-temperature probes. External tetramethylsilane (capillary) was used as reference.

Carbon-13 nuclear magnetic resonance spectra were obtained using a Varian Associates Model XL-100 nmr spectrometer equipped with a Fourier transform accessory, a spin decoupler, and a variable-temperature probe as previously described.[24]

Acknowledgment. Support of this work by the National Science Foundation is gratefully acknowledged.

Registry No.—**7**, 37816-60-7; **8**, 38898-44-1; **9**, 38898-39-4; **10**, 53906-74-4; **13**, 38898-40-7; **14**, 53821-39-9; **18**, 38898-42-9; **19**, 37846-63-2; **20**, 19005-48-2.

References and Notes

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Benzidine Rearrangements. XIII. The Role of Reductive Scission. Reactions of *N,N′*-Dimethylhydrazobenzenes in Acid Solutions[1,2]

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Received September 10, 1974

N,N′-Dimethyl-*p*-hydrazoanisole (**6b**) in acetonitrile containing a small amount of hydrochloric acid underwent reductive scission to *N*-methyl-*p*-anisidine (**7b**, 70%). Other products formed were 2-amino-4-chloro-4′,5-dimethoxy-*N*-methyldiphenylamine (the monodemethylated chloro-o-semidine, **10**, 5%), 2,7-dimethoxyphenazine (**9b**) and 3-chloro-2,7-dimethoxyphenazine (**11**) as a mixture which could not be separated quantitatively, and traces of 4,4′-dimethoxyazobenzene (**12b**). A radical was detected by ESR and is identified as the cation radical of 2,7-dimethoxy-5,10-dimethyl-5,10-dihydrophenazine (**18b**). Anodic oxidation of **6b**, its o-semidine (**8b**), and *N*-methyl-*p*-anisidine each gave rise to the same ESR spectrum, also attributed to **18b**·⁺. *N,N′*-Dimethyl-*p*-hydrazobiphenyl (**6d**) in acetonitrile–hydrochloric acid underwent reduction to *N*-methyl-*p*-aminobiphenyl (90%) along with other unidentified products, some of which contained chlorine. Molecular chlorine was not detected during reaction, and succinonitrile could not be found as a reaction product. A radical was detected during reaction under flow conditions only and its spectrum is attributed to **6d**·⁺ rather than to the analogous dihydrophenazine (**18d**·⁺). *N,N′*-Diethyl-*p*-hydrazoanisole (**16b**) in acetonitrile–hydrochloric acid gave rise to an ESR signal attributed to 2,7-dimethoxy-5,10-diethyl-5,10-dihydrophenazine (**20b**·⁺). In contrast the spectrum obtained with *N,N′*-diethyl-*p*-hydrazobiphenyl (**16d**) is attributed to **16d**·⁺. Our results suggest that the major reducing agent in reductive scission of **6b** is the first-formed rearrangement product, the o-semidine (**8b**), which is in turn oxidized successively to **18b**, **9b**, and **11**. Analogous reactions are believed to occur with **6d**. Oxidative demethylation of **6b** and **6d** also occurs. The results show, also, that the solvent is not a reducing agent in these reactions. The oxidizing agent is either the cation radical (e.g., **7b**·⁺) formed by homolytic scission of the diprotonated hydrazo compound or the protonated hydrazo compound itself.

In spite of the large effort that has been made by numerous research groups over the last few decades, the mechanism of the acid-catalyzed benzidine rearrangements remains unsolved. Of the several mechanisms that have been proposed, the polar transition state one from Ingold, Hughes, and Banthorpe remains the most attractive, although it is by no means universally accepted.[4-6] In recent years, indeed, new proposals for the participation of ring-protonated rather than N-protonated intermediates have been made,[7,8] although there is no direct experimental evidence in support of them as has been pointed out by Banthorpe[9] and by Shine.[10] Apart from the problem of explaining the benzidine rearrangements there are the problems also of accounting for two reactions which accompany benzidine rearrangements. One of these reactions is disproportionation. This accompanies all acid-catalyzed benzidine rearrangements, sometimes to a very small degree and sometimes to an extent far larger than rearrangement itself.[4] The mechanism of disproportionation is quite unknown,[4-6,10,11] and so is the way in which disproportionation and rearrangement may be linked together. Nevertheless, a large number of examples of disproportionation are known and the kinetic boundaries of the reaction have been established.[6,11] The second reaction which accompanies acid-catalyzed benzidine rearrangements is reductive scission, and this has been a much more fugitive and perplexing feature of the overall benzidine rearrangement problem. It is this feature with which we are now concerned.

Disproportionation of hydrazoaromatics leads to a 1:2 mole ratio of azoaromatic and scission amine (eq 1). Reduc-

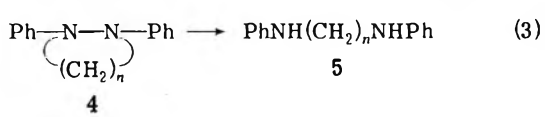
$$\underset{\mathbf{1}}{2\mathrm{ArNHNHAr}} \longrightarrow \underset{\mathbf{2}}{\mathrm{ArN{=}{=}NAr}} + \underset{\mathbf{3}}{2\mathrm{ArNH_2}} \qquad (1)$$

tive scission leads to **3** and is detected when the ratio **3:2** obtained from a hydrazoaromatic is more than eq 1 will accommodate. This was first noticed by Carlin and Wich in their very careful analysis of the products of reaction of *p*-hydrazotoluene with acid,[12] in which it was found that the ratio of the amounts of *p*-toluidine and *p*-azotoluene was a little larger than attainable by eq 1. Carlin and Wich concluded that some of their *p*-hydrazotoluene had undergone reductive scission, and assumed that solvent ethanol was the reducing agent. They did not, however, search for the oxidation product, acetaldehyde, because of the very small amount that would have been formed. Hammond and Clovis[13] confirmed the finding[12] that a small excess of *p*-toluidine was formed, and were also unsuccessful in accounting for the reaction, although they concluded that a transient oxidizing agent of unknown structure was probably associated with the high yield of *p*-toluidine. At the same time the reducing agent responsible for the excess of *p*-toluidine was not designated.

Very little attention has been given to reductive scission since these early reports. It has become noticeable, however, that reductive scission is much more significant in reactions of *N,N'*-dimethylhydrazoaromatics and other hydrazines in which hydrogen is no longer an N substituent. In such compounds, of course, disproportionation into scission amine and azo compound cannot occur. If acid-catalyzed scission of the hydrazo compound did occur, therefore, it is likely that the product would be the scission amine (eq 2). But, again, a reducing agent would have to be involved, too.

$$Ar{-}\underset{\displaystyle R}{\overset{\displaystyle R}{N}}{-}\underset{\displaystyle R}{\overset{\displaystyle R}{N}}{-}Ar \xrightarrow{H^+} \xrightarrow{\text{redn}} 2ArNHR + ? \qquad (2)$$

Reductive cleavage of this kind was noted by Wittig[14] with the cyclic hydrazo compound **4a** (n = 3) which, in 2 *N* hydrochloric acid containing a little ether gave 41% and in benzene–dry HCl gave 50% of *N,N'*-diphenylpropane-1,3-diamine (**5a**), eq 3. These results are of considerable interest, since if the solvent were the reducing agent it would have to be either water or the small amount of ether in the one case, or benzene in the other. Similarly, reaction of **4b** (n = 4) with half-concentrated hydrochloric acid (presumably about 6 *N*) gave, besides rearrangement products, 25.5% of the scission product **5b** (n = 4). In this case, the only solvent was water, and presumably, therefore, the only reducing agents available were water or chloride ion. The reducing agent, however, was not identified.[14] It is noteworthy that in each case of treating **4a** and **4b** with acid a blue color was seen.

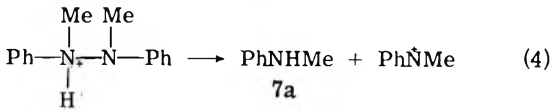


$$Ph{-}N{-}N{-}Ph \longrightarrow PhNH(CH_2)_nNHPh \qquad (3)$$

$(CH_2)_n$ (ring)

4 **5**

Among simpler N,N'-disubstituted hydrazo compounds, *N,N'*-dimethylhydrazobenzene (**6a**) in an aqueous methanol solution of 0.01 *M* hydrochloric acid gave, in White's laboratory, 11% of *N*-methylaniline.[15] An explanation of the reductive scission was not offered. Reductive scission of **6a** was also encountered by Banthorpe with aqueous dioxane containing perchloric acid.[16] Here the formation of *N*-methylaniline (**7a**) was attributed not to reduction, but to protolytic dismutation, eq 4, of which reaction the second

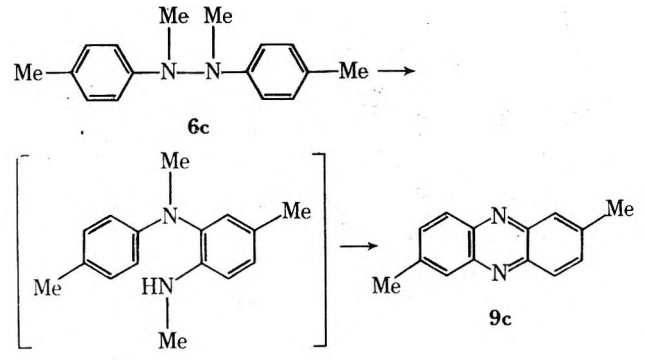


$$Ph{-}\underset{\displaystyle H}{\overset{\displaystyle Me}{N^+}}{-}N{-}Ph \longrightarrow PhNHMe + Ph\overset{+}{N}Me \qquad (4)$$

7a

product, the *N*-methylanilino cation, was presumed to hydrolyze to *N*-methylphenylhydroxylamine. The last compound was thought to be the origin of the small amount of tar formed in the reaction of **6a**.

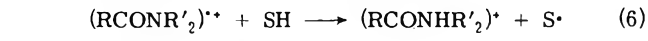
In our own laboratory, two thought-provoking cases were encountered. *N,N'*-Dimethyl-*p*-hydrazoanisole (**6b**) in dioxane–methanol containing hydrochloric acid at 0° gave 46% of rearrangement (to the *o*-semidine) and 42% of scission to *N*-methyl-*p*-anisidine (**7b**).[17] Tarry products were not obtained. Reaction of *N,N'*-dimethyl-*p*-hydrazotoluene (**6c**) in methanolic hydrogen chloride gave a number of products, some of which were not identified, but among which was 2,7-dimethylphenazine (**9c**) in 5% yield. Here, then, we encountered with **9c** a case of oxidative demethylation and oxidative cyclization following, we presumed, rearrangement of **6c** to the *o*-semidine (**8c**), eq 5. We did not find, or look assiduously for, either the rearrangement product **8c** or the scission product, *N*-methyl-*p*-toluidine (**7c**). However, the *o*-benzidine type rearrangement product, 5,5'-dimethyl-2,2'-bis(methylamino)biphenyl (**17c**), was obtained in 8.8% yield.



6c

8c **9c** (5)

In planning to explore further the reactions of *N,N'*-dimethylhydrazoaromatics, and in particular to search for the involvement of solvent in reductive scission, we were guided by some interesting reports in the electrochemical literature. Certain aliphatic amines and amides have been reported to undergo anodic oxidation yet to be recovered essentially without loss. Thus, triethylamine when oxidized anodically in DMSO was recovered as the triethylammonium ion,[18] and a number of amides when oxidized anodically in acetonitrile were recovered in 90–98% yield.[19] Mann interpreted these reactions as involving anodic oxidation of the amine or amide and chemical reduction of the ensuing cation radical by the solvent, e.g., as in eq 6. In the reactions of the amides, S· is the cyanomethyl radical, $\cdot CH_2CN$, and most pleasing, O'Donnell and Mann were able to recover the dimer, succinonitrile, in six amide oxidations in yields of 83–94%. Russell had proposed an identical sequence of reactions for the anodic oxidation of triethylamine in acetonitrile, but did not isolate the succinonitrile.[20]



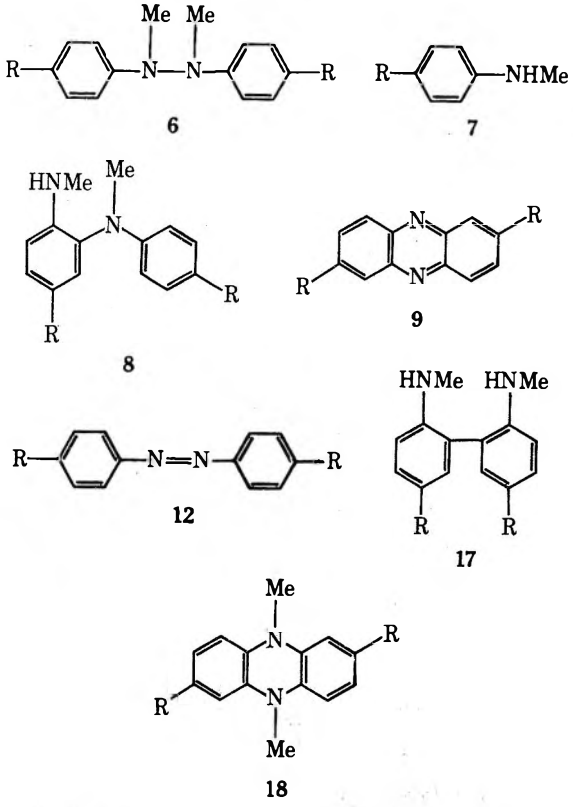
$$(RCONR'_2)^{\cdot+} + SH \longrightarrow (RCONHR'_2)^+ + S\cdot \qquad (6)$$

It was our feeling, therefore, that if reductive scission of hydrazoaromatics could be carried out in acetonitrile solution, and if the solvent were the reducing agent, we should be able to find the oxidation product, succinonitrile, with ease. We have investigated, therefore, the behavior of *N,N'*-dimethyl-*p*-hydrazoanisole (**6b**) and *N,N'*-dimethyl-*p*-hydrazobiphenyl (**6d**) in this solvent. We are able to say at the outset that reductive scission occurred in high yield (>90% with **6d**), but that the solvent does not appear to be involved. Instead, reductive scission is accompanied by an extraordinary series of amino compound oxidation reactions and the formation of cation radicals. We have isolated hitherto unsuspected products of reaction and have applied ESR spectroscopy in our attempts to unravel the courses of reaction.

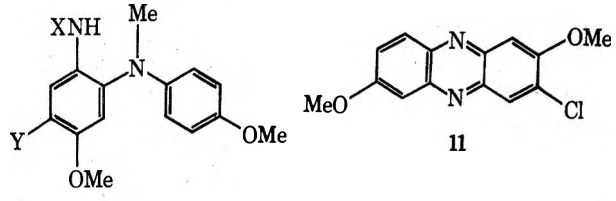
Results. Products of Reaction

Compounds **6–20**, to which reference is frequently made, are listed in the chart of compounds.

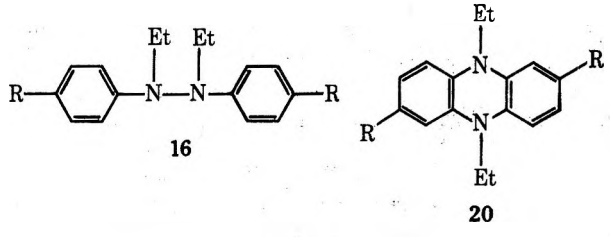
Reactions of *N,N'*-Dimethyl-*p*-hydrazoanisole (6b). Reaction of **6b** with hydrochloric acid in acetonitrile solution was carried out in an ice bath under nitrogen gas. The products were separated by column chromatography and are listed in Scheme I. **7b** was identified by melting point and mixture melting point. The monodemethylated chloro-*o*-semidine (**10**) was identified by the NMR, elemental analysis, and mass spectrum parent peak of its *p*-nitrobenzoyl derivative (**14**), mp 181.5–182.5°. The two phenazines, **9b** and **11**, were obtained as a mixture. Each component



a, R = H; b, R = OMe; c, R = Me; d, R = Ph



10, X = H; Y = Cl
13, X = Y = H
14, X = $O_2NC_6H_4CO$–; Y = Cl
15, X = $O_2NC_6H_4CO$–; Y = H

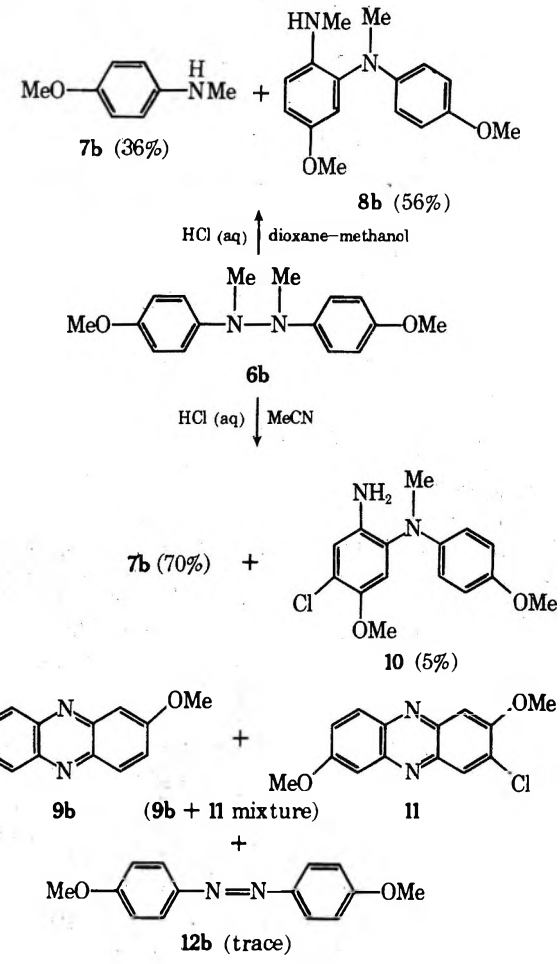


b, R = OMe; d, R = Ph

was separated in low yield and identified by mass spectrum. Thus, **9b** was isolated in 0.3% yield, mp 239.5–241.5°, *m/e* 240.05, and **11** in 0.7% yield, mp 234–237°, *m/e* 274.05. These two compounds were formed in larger yields than those stated, but analysis of the mixture of **9b** and **11** was not successful. *p*-Azoanisole (**12b**) was obtained only in a very small amount and was identified by mp 156–161° and *m/e* 242.1. One other product was isolated, a red solid, mp 189–190°, *m/e* 409.12, but has not been identified.

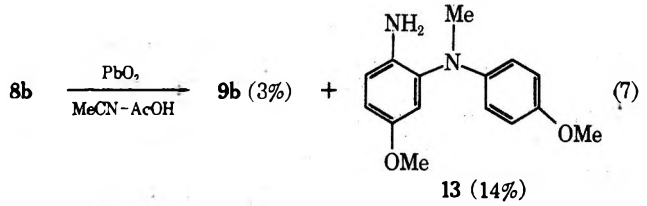
These results differed from those obtained earlier using hydrochloric acid in dioxane–methanol in that a large amount of the o-semidine (**8b**) was obtained earlier.[17] Therefore, the reaction in dioxane–methanol was repeated and a result similar to the earlier one was obtained. That is, **7b** and **8b** were obtained in 36 and 56% yields, respectively, as compared with 42 and 46% formerly. In the present

Scheme I



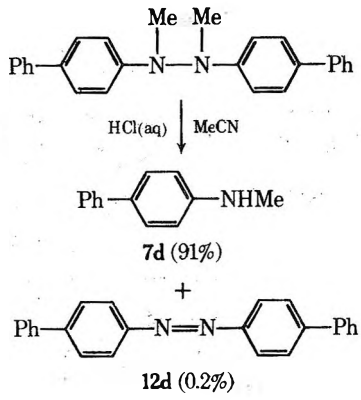
work, however, a small amount (14 wt %) of a purple solid was also obtained which gave a single, broad ESR signal with $g = 2.0036$. This material was not identified.

Oxidation of 8b with PbO_2. Because compounds **9b, 10, 11,** and **12b** most probably arose from oxidations of first-formed **8b,** the direct oxidation of **8b** with PbO_2 in acetic acid–acetonitrile was carried out. After 1.5 hr 27% of **8b** was recovered. Two products, **9b** (3%) and the monodemethylated *o*-semidine (**13,** 14%), were isolated (eq 7). The



latter had been synthesized earlier,[17] and it was identified here as a product by its NMR spectrum and *p*-nitrobenzoyl derivative (**15**), mp 134.5–135°. A third product, mp 155–157°, *m/e* 510.2, was isolated in 13 wt % yield but has not been identified.

Reaction of *N,N'*-Dimethyl-*p*-hydrazobiphenyl (6d). Reaction of **6d** with hydrochloric acid in acetonitrile at 0° was accompanied by a fleeting blue color. After 4 hr the reaction gave *N*-methyl-4-aminobiphenyl (**7d,** 91%) and *p*-azobiphenyl (**12d,** 0.2%), eq 8. **7d** was identified by NMR and its benzenesulfonyl derivative, mp 151–152°, while **12d** was identified by mp 248–250° and *m/e* 334. Three other compounds were obtained, but we have been unable to identify them. One was an oil in 7.6 wt % yield, while the



(8)

other two were solids, mp 134–137°, *m/e* 202 (6.4 wt %), and mp 149–180°, *m/e* 670 (9 wt %). The two solids gave positive Beilstein halogen tests.

Succinonitrile was not found as a product of reaction. Search was made for this product both among the organic products and in the water solution of the beginning work-up procedure. Search was made for succinonitrile directly as a solid and indirectly by infrared (–C≡N band) spectroscopy. No evidence for succinonitrile was found.

Results. ESR Spectra

An ESR spectrum (Figure 1A) was obtained when solutions of **6b** in acetonitrile and hydrochloric acid in acetonitrile were mixed in a gravity flow system just before entering the ESR cell.[21] The color of the solution leaving the cell was pale brown. A similar ESR signal could be detected if the solutions were mixed and the mixture was placed in the cell. The ESR spectrum obtained by flow reaction was at first thought to be of **6b**·$^+$. Guided by the results of anodic oxidation and cyclic voltammetry of **6b,** in which **6b** appeared to be oxidized rapidly to 2,7-dimethoxy-5,10-dimethyl-5,10-dihydrophenazine (**18b**),[22] **18b** was synthesized and oxidized anodically in the ESR cavity and gave an ESR spectrum (Figure 1B) identical with that in Figure 1A. The same spectrum was also obtained by oxidizing the o-semidine **8b** with a solution of **6d** in benzene and acidic acetonitrile under static conditions. Better resolution of ESR spectra was obtained by anodic oxidations of **6b** and **8b.** The better resolved spectrum was also obtained by the anodic oxidation of *N*-methyl-*p*-anisidine (**7b**). All of these spectra suggest that the responsible radical is the cation radical **18b**·$^+$, and that it is formed rapidly in oxidations of **6b, 7b,** and **8b.** This suggestion is supported by cyclic voltammetry results.[22] An identical ESR spectrum was obtained also by the oxidation of **8b** with PbO_2 in acetic acid. Further evidence that the *N,N'*-methyl groups were involved in ESR coupling was obtained from the reaction of **6b**-d_6 in acetone containing hydrochloric acid.

Reaction of **6d** in acetonitrile containing hydrochloric acid gave a fleeting blue color and an ESR spectrum (a_N = 8.98 G) recordable only under flow conditions. In contrast, anodic oxidations of **6d, 7d,** and **8d** gave ESR spectra with a_N = 6.50 G. Cyclic voltammetry[22] showed that **6d** undergoes anodic cyclization to 2,7-diphenyl-5,10-dimethyl-5,10-dihydrophenazine (**18d**). Consequently, it is probable that the ESR spectrum from anodic oxidation of **6d** is due to **18d**·$^+$, whereas that from **6d** in acidic acetonitrile is due to **6d**·$^+$.

Similarly, **16b** in acidic acetonitrile gave the 2,7-dimethoxy-5,10-diethyl-5,10-dihydrophenazine cation radical (**20b**·$^+$), whereas **16d** gave **16d**·$^+$.

Coupling constants obtained with the aid of simulated spectra are given in Table I. These coupling constants can

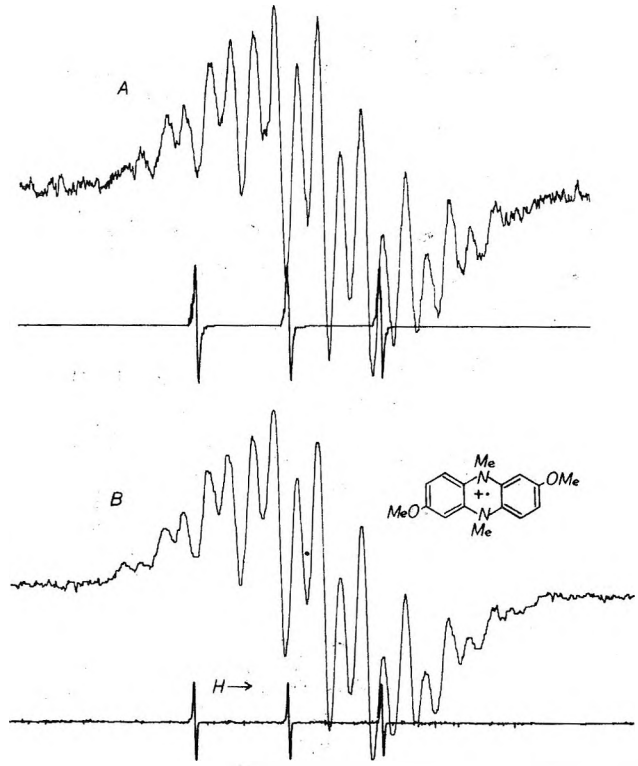


Figure 1. A. ESR spectrum obtained by flow mixing in the ESR cavity 500 ml of an 0.0147 *M* solution of **6b** in MeCN with a solution of 2 ml of concentrated hydrochloric acid in 500 ml of MeCN. The spectrum is attributed to **18b**·$^+$. The standard spectrum is of Fremy's salt, 13-G splitting. B. ESR spectrum of **18b**·$^+$ obtained by anodic oxidation of 2,7-dimethoxy-5,10-dimethyl-5,10-dihydrophenazine (**18b**) in MeCN containing tetra-*n*-butylammonium perchlorate.

be regarded only as approximate. The spectra from which they were measured are not fully resolved, and were either simulated or fitted by stick diagrams with the assumption that the nitrogen and attached alkyl-group coupling constants were equivalent. The simulations were very reasonable agreements, and so were the stick diagrams, but in the absence of fully resolved spectra the coupling constants in Table I can be taken only as guides to the spectra we recorded, yet they do provide some support for our assignments as explained in the Discussion. (See paragraph at end of paper regarding supplementary material.)

Discussion

ESR Spectra. The ESR spectrum (Figure 1A) obtained with solutions of **6b** in acetonitrile–hydrochloric acid appears to be that of the cation radical of 2,7-dimethoxy-5,10-dimethyl-5,10-dihydrophenazine, that is, of **18b**·$^+$. The same spectrum is obtained by anodic oxidation of **18b** itself (Figure 1B). These spectra consist of 19 not-well-resolved lines, to which the central 19 of 23 lines of a stick diagram could be fitted if it were assumed that coupling by only two of the six ring protons in **18b**·$^+$ was detectable, and that couplings by the nitrogen atoms and N substituents were equal. A better resolved spectrum was obtained by the anodic oxidation of **6b,** and of its *o*-semidine (**8b**), and also by the anodic oxidation of *N*-methyl-*p*-anisidine (**7b**), but again no more than 19 lines were obtained.

Resolved ESR spectra of 5,10-disubstituted 5,10-dihydrophenazine cation radicals are not available in the literature for comparison with our results. Well-resolved spectra of 5-methyl-5,10-dihydrophenazine cation radical (so-called MPH·$^+$) have been reported but not analyzed.[23,24] Well-resolved spectra of the parent 5,10-dihydrophenazine

Table I
ESR Parameters

Reaction	Figure[e]	Radical	g	a_{2N}	a_{R_1}	a_{R_2}	a_{2H}
6b, HCl–MeCN	1A	**18b**$^{\cdot+}$	2.0033	6.24	6.24[a]	6.24[a]	2.69[b]
18b, anodic oxidn	1B	**18b**$^{\cdot+}$					
8b, anodic oxidn	3	**18b**$^{\cdot+}$		6.18	6.18[a]	6.18[a]	2.59[b]
6b-d_6, HCl–MeCN	4A	**18b**-$d_6^{\cdot+}$	2.0035	6.69			
13, PbO_2–AcOH	5A	**19b**$^{\cdot+}$		6.29	6.29[a]	[c]	2.60[b]
6d, HCl–MeCN	6A	**6d**$^{\cdot+}$	2.0034	8.98	8.98[a]	8.98[a]	
6d, anodic oxidn	7A	**18d**$^{\cdot+}$		6.50	6.50[a]	6.50[a]	
8d, anodic oxidn		**18d**$^{\cdot+}$		6.50	6.50[a]	6.50[a]	
16b, HCl–MeCN	8A	**20b**$^{\cdot+}$	2.0034	6.34	3.19[d]	3.19[d]	3.19[b]
16d, HCl–MeCN	9A	**16d**$^{\cdot+}$	2.0038	8.14	8.14[d]	8.14[d]	

[a] *N*-Methyl group. [b] 3,8 hydrogens. [c] N–H proton unresolved. [d] Methylene hydrogens in *N*-ethyl group. [e] See paragraph at end of paper regarding supplementary material.

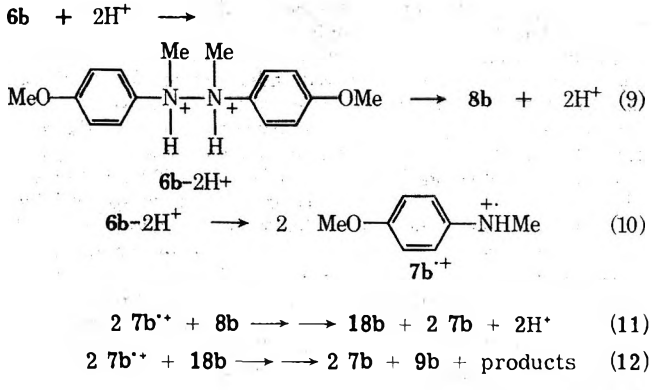
cation radical itself have been reported,[25,26] and complete analysis[27] gives a_N = 6.14 G, a_{NH} = −6.49 G, a_{H_1} = 0.66 G, and a_{H_2} = −1.71 G. That is, the hydrogen atoms in the 2, 3, 7, and 8 positions of the ring have the larger coupling, and the a_N and a_{NH} couplings are very close (earlier analysis had them as equal[26]).

Cauquis, Genies, and Serve[28] have summarized data for cation radicals obtainable from tetraphenylhydrazine (TPH). Among these is TPH$^{\cdot+}$ itself (a_N = 7.9,[28] 7.25 G[29]), and 5,10-diphenyl-5,10-dihydrophenazine cation radical (a_N = 6.4 G).

These data support our analysis for **18b**$^{\cdot+}$, that $a_N = a_{N-Me} \simeq 6$ G, and coupling from only two hydrogens is detected. How valid our coupling constant is for these (2.69 G) can only be settled, however, with better resolved spectra.

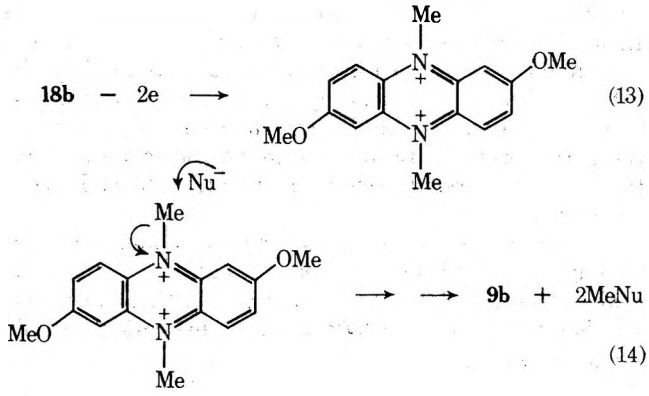
Similarly, dihydrophenazine cation radicals appear to be formed by anodic oxidation of **6d** and **8d** (giving **18d**$^{\cdot+}$, a_N = 6.50 G), and by reaction of **16b** in acidic acetonitrile (giving **20b**$^{\cdot+}$, a_N = 6.34 G). In contrast, **6d** in acidic acetonitrile appears to give **6d**$^{\cdot+}$ (a_N = 8.9 G), and **16d** to give **16d**$^{\cdot+}$ (a_N = 8.14 G).

Products and Course of Reaction. Two major structural changes occur in **6b** in acidic solution. These are rearrangement to the o-semidine (**8b**) and scission to the amine (**7b**). Once **8b** has been formed it becomes a reducing agent available for participation in reductive scission of **6b**, since there can be little doubt that **8b** is the origin of the phenazines, **9b** and **11**, which we have isolated. Furthermore, there can be little doubt, also, that interposed between **8b** and these phenazines is the formation of 2,7-dimethoxy-5,10-dimethyl-5,10-dihydrophenazine (**18b**), detectable as its cation radical (**18b**$^{\cdot+}$), although not itself isolated.



These major events can be expressed as in eq 9–12, but these equations are most likely an oversimplification. Intramolecular rearrangement of **6b** to **8b** is to be expected. Whether or not diprotonated **6b** also cleaves homolytically to **7b**$^{\cdot+}$ is not certain, although it is an attractive idea. We have not detected the formation of **7b**$^{\cdot+}$ by ESR, and therefore we cannot rule out the possibility that protonated or diprotonated **6b** may be reduced directly.

Reduction of **6b** to **7b** is a two-electron process. After the rearrangement of **6b** to **8b** (which is not a redox process) occurs, two oxidative sequences would lead to **9b**. The first of these (eq 11) is a two-electron process, while the second (the demethylation of **18b**) can also be written most simply as a two-electron process, in which the oxidation steps (the formation of **18b**$^{2+}$) are followed by nucleophilic removal of the methyl groups (eq 13 and 14). Other than the formation



of **9b**, we have no evidence that the methyl groups are removed in this way. It may be that they are removed also from **8b** before the formation of **18b**, as suggested by the formation of **10**, Scheme I, but the overall electron balance between **8b** and **9b** will be the same. It is also possible that demethylation is itself an oxidation process, that is, that the methyl groups are eventually converted into formaldehyde.

This redox balance presents us with a problem in accounting entirely for the reductive scission of **6b** (and, below, **6d**). If oxidative cyclization and demethylation of **8b** were the only way of supplying electrons to **6b**, we would expect to see much larger amounts of **9b** than we do. That is, there should be 4 mol of **7b** per mol of **9b**, and the amount of **7b** is far in excess of that. At the same time, however, other oxidation products (**11** and **12b**, Scheme I) which were isolated indicate that other, but related, sources of electrons were available for the reduction of **6b**.

The chlorination products **10** and **11** represent oxidation stages, and in so doing add to the overall redox balance another two-electron stage per chlorine atom introduced into the ring. These products do not appear to come from reac-

tion of molecular chlorine, however, since tests for the formation of chlorine (in reactions of **6d**, below) were negative. Instead, it appears that nucleophilic attack of chloride ion on oxidatively formed cations is the source of **10** and **11**.

In addition, the separation and isolation of oxidation products was difficult and by no means quantitative. Some of the oils from which oxidation products were isolated remained uncharacterizable and unidentified.

Our summation of the reactions of **6b** is that reductive scission can be explained with the formation of **18b** and the several other products of oxidation (**9b, 10, 11, 12b**), even though the quantitative results are not as good as we would like.

Reactions of **6d** are more of a problem, but again we feel that reductive scission must have the same origins as those of **6b**. The large yield of *N*-methyl-4-aminobiphenyl (**7d**, 91%) means that oxidations must be very extensive. Products were obtained, two of which contained chlorine, but we have been unable to identify them. The only oxidation product identified, but obtained in very small yield, was the azo compound (**12d**, 0.2%).

In these reductive scissions chloride ion is a potential reducing agent (eq 15). It is an attractive possibility, since

$$2R_2NH^{\cdot+} + 2Cl^- \longrightarrow 2R_2NH + Cl_2 \qquad (15)$$

some cation radicals (e.g., of perylene[30]) oxidize chloride ion to chlorine. However, molecular chlorine was not found in the reactions of **6d** in acetonitrile–hydrochloric acid. Ledwith[31] has shown that the tris(*p*-bromophenyl)amine cation radical reacts with chloride ion, and becomes monochlorinated either directly or *via* disproportionation, much in the way that chloride ion reacts with the phenothiazine cation radical[32] and N-substituted phenothiazine cation radicals.[33] Chlorine is not formed in these reactions, and the products are formed by entry of chloride ion into the cation radical or corresponding dication. The same route(s) appear to be responsible for the chlorination products in the present work. Therefore, the only reducing agents identifiable in the present reactions appear to be **8b** and its descendants.

The deductions we have made about reactions of **6b** and **6d** apply also, we believe, to those of **6a**[17] and of the ethyl analogs **16b** and **16d**. In addition, it may be that **6d** and **16d** are themselves oxidized by scission amine cation radicals (e.g., **7d**$\cdot^+$, eq 16).

$$\mathbf{7d}^{\cdot+} + \mathbf{6d} \longrightarrow \mathbf{7d} + \mathbf{6d}^{\cdot+} \qquad (16)$$

It is possible that we have missed small amounts of succinonitrile in our search for solvent involvement. The situation remains, however, that the only reducing agents that we *have* been able to find are the o-semidines, their cyclized descendants, and, to a very small extent, the hydrazo compounds themselves (*via* their demethylation).

As far as we know, our results with *N*-alkyl-*N*-arylhydrazoaromatics are the first of their kind. Reactions of tetraarylhydrazines with acids were described long ago by Wieland. In fact, reaction of tetra-*p*-tolylhydrazine led to di-*p*-tolylamine, 2,7-dimethyl-5,10-di-*p*-tolyl-5,10-dihydrophenazine, and also its dichlorination product.[34,35] The reactions of tetraphenylhydrazine with acids are complicated but not unlike those we have discussed, and lead in various circumstances to rearrangement and the formation of polymers,[36–38] to the tetraphenylhydrazine cation radical and the cation radical of the rearrangement product (*N,N,N'*-triphenyl-*p*-phenylenediamine),[29] and to the cation radical of 5,10-diphenyl-5,10-dihydrophenazine.[28,39] Thus, the reactions we have observed are part of the general chemistry of hydrazoaromatics, and are likely to occur as side reactions when hydrazoaromatics rearrange. Benzidine rearrangements have never been found to be intermolecular. There are proposals that cation radicals are involved in the intramolecular rearrangements,[4] but these have little or no experimental support. If scission of protonated tetraarylhydrazoaromatics leads to diarylaminium radicals,[35,36] we might expect that they may recombine as rearrangement products. Cauquis has proposed a similar recombination in the reaction of perchloric acid with triphenylhydrazine.[40] We might expect the same behavior of our *N*-alkyl-*N*-arylaminium radicals if they are formed as in eq 10. These several recombinations would constitute *intermolecular* benzidine rearrangements. Because there is no direct evidence, as yet, that benzidine rearrangements are anything but intramolecular, we would conclude that where it accompanies a benzidine rearrangement as a minor event, reductive scission may involve the protonated hydrazoaromatic directly. On the other hand the reason that reductive scission is so rarely seen along with benzidine rearrangements may well be that reductive scission requires cation radicals, and that it is these that are rarely formed in benzidine rearrangements. Certainly, the possibility that intermolecular rearrangements may occur in tetrasubstituted hydrazoaromatics such as compounds **6** and the tetraaryl analogs is most intriguing.

Experimental Section

N,N'-Dimethyl-*p*-hydrazoanisole (**6b**), *N,N'*-dimethyl-*p*-hydrazobiphenyl (**6d**), the scission amines (**7b, 7d**), the o-semidines (**8b, 8d**), the azo compounds (**12b, 12d**), and 6-amino-3,4'-dimethoxy-*N*-methyldiphenylamine (the demethylated o-semidine, **13**) have been described earlier.[17]

***N,N'*-Dimethyl-d_6-*p*-hydrazoanisole (6b-d_6).** A solution of 4 g (16.4 mmol) of *p*-hydrazoanisole in 100 ml of dry THF was added to 3.5 ml of commercial 90% *n*-butyllithium in hydrocarbon solvent until the mixture became orange yellow. To this was added 5.6 g (38.7 mmol) of MeI-d_3 in 20 ml of THF. The solution was stirred for 2 hr, diluted with ether, washed with 10% NaOH and water, and worked up after drying over K_2CO_3 to give 4.31 g (95%) of **6b**-d_6, mp 104–106°.

***N,N'*-Diethyl-*p*-hydrazoanisole (16b).** The procedure above was used with 6.54 g (26.2 mmol) of *p*-hydrazoanisole, 5 ml of *n*-BuLi, and EtBr, to give 7.7 g (96%) of **16b** as an oil. This was treated with active carbon in cyclohexane and obtained again as an oil, NMR (CCl_4) δ 1.67 (t, 6 H), 3.36 (q, 4 H), 3.63 (s, 6 H), 6.69 (s, 8 H).

Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 72.0; H, 8.05; N, 9.33. Found: C, 71.8; H, 8.04; N, 9.54.

***N,N'*-Diethyl-*p*-hydrazobiphenyl (16d).** The same procedure was used with 6.9 g (20.5 mmol) of *p*-hydrazobiphenyl, 5 ml of *n*-BuLi solution, and EtBr to give 6.89 g (86%) of **16d**, mp 126–127° (from ethanol–ether), NMR (CCl_4) δ 1.29 (t, 6 H), 3.57 (q, 4 H), 7.75 (d, 4 H), 7.5 (m, 14 H).

Anal. Calcd for $C_{28}H_{28}N_2$: C, 85.7; H, 7.19; N, 7.14. Found: C, 85.8; H, 7.21; N, 7.16.

Reaction of 6b in Acidic Dioxane–Methanol. To a cold solution of 250 mg (0.92 mmol) of **6b** in 10 ml of dioxane and 40 ml of methanol was added 0.1 ml of concentrated HCl in 10 ml of methanol. The brown solution was stirred under nitrogen for 30 min on an ice bath and quenched with ammonia gas. The solvent was removed at room temperature on a rotary evaporator, and the residue was triturated with benzene to leave 90 mg of a purple, paramagnetic solid. Evaporation of the benzene gave 230 mg of brown oil. The oil was assumed to be a mixture of *N*-methyl-*p*-anisidine (**7b**) and the *o*-semidine (**8b**).[17] Quantitative analysis by NMR spectroscopy gave yields of 36% of **7b** and 56% of **8b** from this reaction of **6b**. The purple solid was dissolved in basic, aqueous NaI solution. Extraction with ether gave 36 mg of a brown oil whose NMR spectrum indicated one methyl and two methoxy groups. A *p*-nitrobenzoyl derivative was obtained, and was not that of 2-amino-4',5-dimethoxy-*N*-methyldiphenylamine (**13**). The brown oil remains unidentified.

2,7-Dimethoxy-5,10-dimethyl-5,10-dihydrophenazine (18b). 2,7-Dimethoxyphenazine (**9b**) was made by boiling for 6 hr under nitrogen a mixture of 10 g of *p*-nitroanisole, 10 g of *p*-anisidine,

and 30 g of powdered KOH. Instead of steam distilling,[41] the mixture was poured into water and stirred with 500 ml of benzene. The organic layer was washed with water until the washings were almost colorless, dried, and evaporated to give an oily residue. Trituration with benzene gave 2.1 g of yellow solid which was boiled with 40 ml of acetic anhydride (to convert the phenazine *N*-oxide into the phenazine). The cool solution was poured into water which was then neutralized and extracted with chloroform, which gave a brown oil. Crystallization from benzene gave 920 mg (4.7%) of **9b**, mp 246–247° (lit.[41] mp 246°).

Crude **9b** (711 mg, 2.98 mmol) was methylated in dry dimethoxyethane with potassium and methyl iodide. Work-up gave some unused **9b** and, by chromatography on alumina, 86 mg of *p*-azoanisole and 100 mg (12.5%) of **18b**, mp 142–142.5° (from ether), NMR (acetone-d_6) δ 3.66 (s, 9 H), 6.01 (s, 3 H), and 6.25 (br s, 6 H).

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.1; H, 6.71; N, 10.4. Found: C, 71.0; H, 6.78; N, 10.6.

Reaction of 6b in Acidic MeCN. Cold solutions of 2 g (7.35 mmol) of **6b** in 100 ml of MeCN and of 2 ml of 12 *N* HCl in 50 ml of MeCN were mixed and stirred under N_2 for 1 hr while in an ice bath. The only color observed on mixing was light brown. The mixture was quenched with 30 ml of 10% NaOH and diluted with 200 ml of ether. The ether layer, after washing with 2 × 50 ml of 10% NaOH and with water and drying over K_2CO_3, gave 2.17 g of brown oil.

The alkaline water layer was acidified with 10% HCl, neutralized with $NaHCO_3$, and extracted with ether to give 64 mg of **7b**, identified by TLC and NMR. The aqueous layer appeared not to contain an aminophenol.

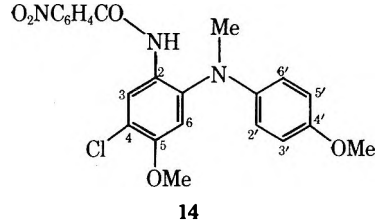
The brown oil was triturated with benzene and deposited 7 mg of a yellow solid, mp 234–237°. This solid gave a positive Beilstein halogen test. The mass spectrum showed peaks at *m/e* 240.05 and 274.05. The former corresponds with **9b** and the latter with **11**. The melting point of this solid indicated that it was mostly **11**, contaminated with **9b**.

The benzene filtrate (from the trituration) was chromatographed on alumina (Woelm activity III, 2.2 × 33 cm). Elution with petroleum ether (300 ml, bp 30–60°) was ineffective. Elution with petroleum ether–ether mixtures gave a sequence of fractions as follows: 2 l. of 95:5, fractions 4–27; 500 ml of 90:10, fractions 28–33; 500 ml of 80:20, fractions 34–39; 1.5 l. of 50:50, fractions 40–57; and 700 ml of ether, fractions 58–66. Fractions 5–7 gave 17 mg of yellow oil from which was crystallized a trace of **12b** from ethanol, mp 156–161° (lit.[17] mp 158°), *m/e* 242.2. Fractions 8–37 gave 1.34 g of **7b**, mp 35–36° (from *n*-hexane), mmp 35–37°. This with the earlier portion is a 70% total yield of **7b**.

Fractions 38–44 gave 160 mg of an oily solid. This was triturated with benzene to give 6 mg of yellow solid which was sublimed at 170° (25 mm) to give 3 mg of **9b**, mp 239.5–241.5°, *m/e* 240.05; this solid was contaminated with traces of **11**. The benzene filtrate was concentrated to give 10 mg of impure **11**. This was sublimed and crystallized from benzene to give impure **11**, mp 234–237°, *m/e* 274.05. The product gave a positive Beilstein halogen test. The benzene concentrate was evaporated and the residue was triturated with *n*-hexane, and the *n*-hexane filtrate gave 106 mg of yellow oil. The oil appeared to be a single compound and is believed to have been 2-amino-4-chloro-4',5-dimethoxy-*N*-methyldiphenylamine (the monodemethylated chloro-*o*-semidine, **10**), in which case its yield was 5%. The *p*-nitrobenzoyl derivative (**14**) of **10** had mp 181.5–182.5 (from ether) and *m/e* 441.1

Anal. Calcd for $C_{22}H_{20}N_3O_5Cl$: C, 59.8; H, 4.53; N, 9.51; Cl, 8.03. Found: C, 59.8; H, 4.68; N, 9.77; Cl, 8.21.

Assignment of the position of the chlorine atom in **10** was made by comparing the NMR spectrum of **14** with that of the *p*-nitrobenzoyl derivative (**15**) of 2-amino-4',5-dimethoxy-*N*-methyldiphenylamine (**13**). The NMR ($CDCl_3$) of **14** follows: δ 3.27 (s, 3 H), 3.73, 3.83 (2 s, 6 H), 6.75 (s, 5 H), 7.58 (d, 2 H), 8.14 (d, 2 H), 8.33, 8.53 (2 s, 2 H). The NMR of **15** (see later) had a 1 H singlet at δ 8.45 (assigned to proton 6) and a 6 H singlet at δ 6.73 assignable to the remaining numbered ring protons. These correspond with the



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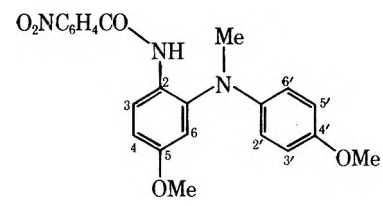

15

5 H singlet (2', 3', 3, 5', 6' protons) at δ 6.75 and the 1 H singlet at δ 8.53 in **14**. The sharpening of the singlet at δ 8.53 in 14 is assigned to proton 6.

Reaction of 6d in Acidic MeCN. A. A cold solution of 1.3 ml of concentrated HCl in 20 ml of MeCN was added to a cold suspension of 1 g (2.74 mmol) of **6d** in 80 ml of MeCN. The mixture turned blue and became brown within 1 min. Stirring in an ice bath under N_2 was continued for 4 hr. The solution was neutralized with 10% KOH, and the organic layer was evaporated at reduced pressure. The residue was taken up in $CHCl_3$ dried over K_2CO_3 to give 1.27 g of a brown oil, whose ir spectrum failed to indicate the presence of –C≡N groups.

The oil was chromatographed on silica gel (Davison 950, 60–200 mesh, 2.2 × 28 cm) with petroleum ether–ether elution. Five hundred milliliters of 98:2 gave 56 mg of orange-red solid from which trituration with ethanol–CCl_4 gave 2 mg (0.2%) of **12d**. One thousand milliliters of 97:3 gave 76 mg of an oil which could not be identified. One and five-tenths liters of 95:5 gave 910 mg (91%) of **7d**, identified by NMR, ir, and benzenesulfonyl derivative, mp 151–152° (lit.[17] mp 152–153°). Five hundred milliliters of 90:10 gave 64 mg of a solid, mp 134–137° (from MeCN), *m/e* 202. Two hundred milliliters of ether gave 90 mg of a solid, mp 149–180° (from MeCN), *m/e* 670. The last two solids gave positive Beilstein halogen tests, but remain unidentified.

B. Reaction was repeated and the mixture was neutralized with 6 ml of concentrated NH_4OH. The solvent was removed as before and the residue was dissolved in CCl_4 in which succinonitrile is poorly soluble. The CCl_4 solution was washed twice with water, in which succinonitrile is soluble. The water solution was evaporated at 40° and after the residue was dried (in $CHCl_3$) its ir spectrum gave no evidence of –C≡N groups.

Oxidation of 8b with PbO_2. A solution of 500 mg (1.84 mmol) of **8b** in 20 ml of MeCN and 0.7 ml of AcOH was stirred with 1 g of PbO_2 in an ice bath under N_2 for 1.5 hr. After the AcOH was neutralized the mixture was worked up to give 400 mg of brown oil, which was chromatographed on alumina (Woelm activity III, 1.7 × 29 cm). A series of 75-ml fractions of petroleum ether–ether eluates was collected. Fractions 7–10 (90:10) gave 135 mg of recovered **8b**, identified by NMR and mp 60–60.5° (from *n*-hexane). Fractions 11–31 (85:15) gave 115 mg of solid. Crystallization from benzene gave 14 mg (3%) of **9b**, mp 248–249.5°, *m/e* 240.09. Evaporation of the benzene filtrate gave 64 mg (14%) of **13**, identified by NMR.[17] The *p*-nitrobenzoyl derivative (**15**) of 13 had mp 134.5–135° (from ethanol) and NMR ($CDCl_3$) δ 3.25 (s, 3 H), 3.73, 3.78 (2 s, 6 H), 6.73 (s, 6 H), 7.54 (d, 2 H), 8.13 (d, 2 H), 8.26 and 8.4 (2 s, 2 H).

Anal. Calcd for $C_{22}H_{21}N_3O_5$: C, 64.9; H, 5.20; N, 10.3. Found: C, 64.9; H, 5.23; N, 10.3.

Fractions 32–38 (ether) gave 65 mg of solid. Crystallization from *n*-hexane–ether gave mp 155–157°, *m/e* 510.2. This compound remains unidentified.

Reaction of 6b with D_2SO_4 in Acetone-d_6. Search for CIDNP. A solution of 109 mg of D_2SO_4 in 0.5 ml of acetone-d_6 was made and added to 0.3 ml of acetone-d_6 containing a weighed sample for investigation, and the NMR spectrum was scanned over a period of time in a Varian A-60 spectrometer. The NMR spectrum was compared with that of an identical solution made without D_2SO_4. Samples of **7b** and **8b** were used as controls. When **6b** and **6b**-d_6 were used in D_2SO_4 solution, the only NMR signals observed were those of **7b**. No enhanced absorption or emission lines were observed, and the *o*-semidine (**8b**) signals were not observed either.

ESR Spectra. Three techniques were used. In the flow reactions, the substrate solution and solution of acid in the same solvent were allowed to flow by gravity into a mixing chamber inserted into a Varian Associates flat cell. Before flowing the solutions were purged with N_2. Static chemical oxidations were carried out with the apparatus in Figure 2. Tubes A and B were charged with reactants, degassed by freeze–thaw technique, and mixed for transfer to the esr capillary. Occasionally, a break-seal was placed

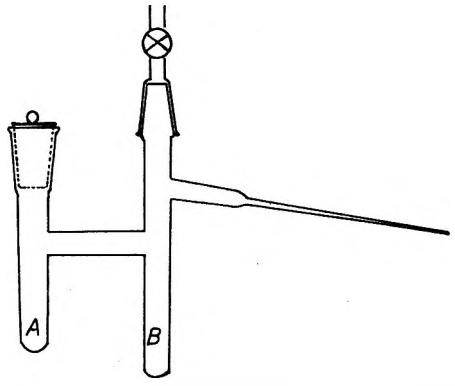

Figure 2. Apparatus for recording ESR spectra in static oxidations. Occasionally tubes A and B were separated by a break-seal and arranged appropriately for degassing.

between A and B. Anodic oxidations were carried out with a Varian Associates flat cell and Pt gauze anode.

A copper wire was inserted into the upper neck of the cell. Reference cells were not used. An applied voltage of about 2.5 V at 30 μA was used, and no attempt was made to seek refined or optimum conditions.

Registry No.—**6b,** 30724-67-5; **6b-d_6,** 53731-00-3; **6d,** 30788-03-5; **7b,** 5961-59-1; **8b,** 30745-00-7; **8d,** 30724-70-0; **9b,** 5051-19-4; **10,** 53731-01-4; **11,** 53731-02-5; **12b,** 501-58-6; **13,** 30788-10-4; **14,** 53731-03-6; **15,** 53731-04-7; **16b,** 53731-05-8; **16d,** 53731-06-9; **18b,** 53731-07-0; MeI-d_3, 865-50-9; EtBr, 74-96-4; *p*-hydrazobiphenyl, 4088-58-8; *p*-hydrazoanisole, 1027-40-3.

Supplementary Material Available. Figures 3–9 listed in Table I will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-703.

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A Kinetic Study of the Acid-Catalyzed Disproportionation of an Unsymmetrical Disulfide[1]

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Received October 16, 1974

The disproportionation of benzyl *p*-tolyl disulfide into an equilibrium mixture of *p*-tolyl and benzyl disulfides has been studied kinetically by an NMR method at 70° in acetic acid–1% H_2O containing 0.05–0.20 *M* sulfuric acid. The important experimental findings are as follows: (1) the reaction is subject to marked catalysis by added strong acid; (2) the kinetics show a second-order dependence on disulfide concentration; (3) the reaction can be effectively completely inhibited for significant periods of time by the addition of very small amounts of either *p*-toluenethiol or benzyl mercaptan, with the rate after the inhibition period being the same as in the absence of added mercaptan; (4) the reaction can be markedly accelerated by the addition of small amounts of *n*-butyl sulfide. The results seem to be best explained by a chain-type mechanism involving *ionic* intermediates. In the case of the ordinary acid-catalyzed disproportionation the chain-propagating steps involve nucleophilic attack by the disulfide on dithiosulfonium ions **2** and **3**. In the case of the *n*-butyl sulfide catalyzed reaction the propagating steps are thought to involve attack of the disulfide on di-*n*-butylthioalkylsulfonium ions (**4** and **5**).

Unsymmetrical disulfides undergo disproportionation (eq 1) under a variety of conditions. The mechanism for

$$2RSSR' \rightleftharpoons RSSR + R'SSR' \quad (1)$$

disproportionation in alkaline solution is believed[2,3] to involve a chain sequence of displacements on the disulfide by mercaptide ions (eq 2), which are themselves formed as one product of the alkaline hydrolysis of a small fraction of the disulfide.

$$RS^- + RSSR' \longrightarrow RSSR + R'S^- \quad (2a)$$

$$R'S^- + RSSR' \longrightarrow R'SSR' + RS^- \quad (2b)$$

The mechanism of the acid-catalyzed disproportionation is much less certain. Both Ryle and Sanger[3] and Benesch and Benesch[4] found that the disproportionation in HCl solutions was strongly inhibited by the addition of mercaptans. The rate also dropped off markedly with a decrease in HCl concentration. Neither group investigated whether catalysis by other mineral acids was more or less effective. Benesch and Benesch[4] observed that the disproportionation could be catalyzed by added alkyl or aryl sulfenyl chlorides and by hydrogen peroxide. In both investigations the data were presented as plots of percent disproportionation vs. time, and neither rate constants nor reaction order were determined. Both sets of authors proposed a chain-type mechanism (eq 3) for the acid-catalyzed disproportionation involving sulfenium ions as the key intermediate. This

$$RSSR' + H^+ \rightleftharpoons RS^+ + R'SH \quad (3a)$$

$$RS^+ + RSSR' \longrightarrow RSSR + R'S^+ \quad (3b)$$

$$R'S^+ + RSSR' \longrightarrow R'SSR' + RS^+ \quad (3c)$$

scheme seemed to fit well with the marked inhibition of the reaction by mercaptan, and also with the acceleration by added sulfenyl chlorides, since at that time sulfenyl chlorides were thought to form sulfenium ions fairly readily, something that we now know is not the case.[5]

Fava and Reichenbach[6] have investigated the acid-catalyzed exchange of radioactive thiophenol and phenyl disulfide (eq 4). They found that although HCl, HBr, or HI were

$$PhS^*H + PhSSPh \overset{H^+}{\rightleftharpoons} PhS^*SPh + PhSH \quad (4)$$

catalysts for the exchange, perchloric acid had no appreciable effect. Moreover, the relative catalytic effectiveness of the halogen acids was strongly dependent on the halogen in a manner that suggested that the anion of the acid played a key role as a nucleophile in the mechanism of the reaction.

These results and the formal kinetics of the reaction led to the proposal of the mechanism shown in eq 5 for the acid-catalyzed exchange. Cuiffarin and Fava[7] have pointed out

$$PhSSPh + HX \rightleftharpoons PhS\overset{+}{S}(H)Ph + X^- \quad (5a)$$

$$X^- + PhS\overset{+}{S}(H)Ph \xrightarrow[\text{determining}]{\text{rate}} PhSX + PhSH \quad (5b)$$

$$PhS^*H + PhSX \longrightarrow PhS^*SPh + H^+ + X^- \quad (5c)$$

that the mechanism observed for this exchange suggests that the HCl-catalyzed disproportionation of disulfides could well involve the mechanism shown in eq 6, rather

$$RSSR' + H^+ \rightleftharpoons RS\overset{+}{S}(H)R' \quad (6a)$$

$$Cl^- + RS\overset{+}{S}(H)R' \rightleftharpoons RSCl + R'SH \quad (6b)$$

$$RSCl + RSSR' \rightleftharpoons RS\overset{+}{S}(R)SR' + Cl^- \rightleftharpoons RSSR + R'SCl \quad (6c)$$

$$R'SCl + RSSR' \rightleftharpoons RS\overset{+}{S}(R')SR' + Cl^- \rightleftharpoons R'SSR' + RSCl \quad (6d)$$

than the one involving sulfenium ion intermediates favored by Ryle and Sanger[3] and Benesch and Benesch.[4]

We felt that a further kinetic study of the acid-catalyzed disproportionation of an unsymmetric disulfide under appropriate conditions might be able to cast further light on the question of the mechanism of the reaction. Benzyl *p*-tolyl disulfide (**1**), p-$CH_3C_6H_4SSCH_2Ph$, seemed a particularly good substrate to use, since the singlet for the methylene protons in this disulfide occurs at somewhat different field, δ 3.83 ppm, than the singlet for the methylene protons of its disproportionation product, benzyl disulfide, 3.48 ppm.[8] Because of this one can follow the course of this particular disproportionation continuously by monitoring the relative intensity of the two different methylene peaks in a sample of the reaction solution contained in a thermostated nmr probe. In studying the acid-catalyzed disproportionation we also felt it desirable, in view of the experience of Fava and Reichenbach,[6] to use as a catalyzing acid

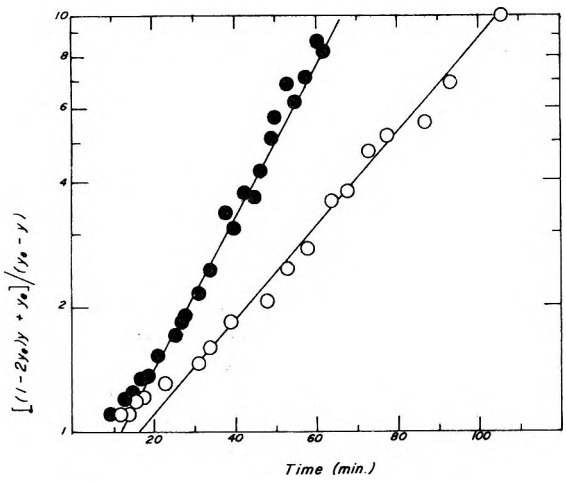


Figure 1. Kinetic data for the disproportionation of 1 in acetic acid–0.56 *M* H_2O containing 0.10 *M* H_2SO_4 plotted according to eq 9. ●, initial concentration of 1, 0.30 *M*; ○, initial concentration of 1, 0.20 *M*.

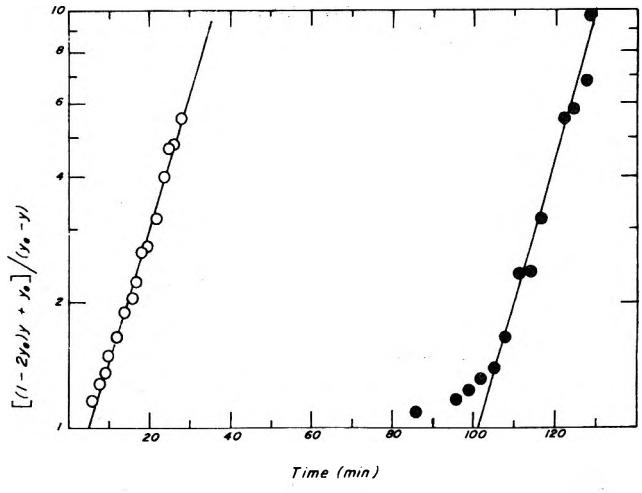


Figure 2. Effect of added thiol on the kinetics of the disproportionation of 1. Data plotted according to eq 9. Both runs in acetic acid–0.56 *M* H_2O as solvent with 0.15 *M* H_2SO_4 and an initial concentration of 1 of 0.30 *M*. ●, 3.6×10^{-4} *M* *p*-toluenethiol added; ○, no added thiol.

one whose conjugate base was not significantly nucleophilic.

For these reasons the specific system chosen for study was the disproportionation of benzyl *p*-tolyl disulfide (eq 1, R = $PhCH_2$, R′ = *p*-$CH_3C_6H_4$) in acetic acid–0.56 *M* water containing 0.05–0.20 *M* H_2SO_4 as acid catalyst. Despite the fact that the reaction can be followed continuously by NMR, the quality of the kinetic data was not as high as we had originally hoped. However, the kinetic data are of sufficient precision, and, in particular, the effects of certain additives are sufficiently striking that certain characteristics of the reaction are clearly apparent. These do provide some definite and useful insights into the mechanism of the acid-catalyzed disproportionation.

Results

The disproportionation of 1 was followed by observing the change in the relative intensity of the separate nmr signals for the methylene hydrogens of *p*-$CH_3C_6H_4SSCH_2Ph$ (1) and $PhCH_2SSCH_2Ph$ in solutions initially 0.20 or 0.30 *M* in 1. Acetic acid–0.56 *M* water containing 0.05–0.20 *M* H_2SO_4 as the strong acid catalyst was the solvent. All runs were carried out at 70°.

Equilibrium Constant for the Disproportionation of 1. The disproportionation is an equilibrium, and equilibrium is reached when the concentration of 1 is about twice that of $PhCH_2SSCH_2Ph$. For each run the equilibrium constant, K_e, for the disproportionation, expressed as

$$K_e = \frac{[R'SSR'][RSSR]}{[RSSR']^2} \qquad (7)$$

was determined from measurements of the relative areas of the two peaks made 24 and 48 hr after the initiation of the reaction. There was no significant change in the relative peak areas during the second 24 hr, indicating that the reaction definitely reached equilibrium during the first 24 hr. As expected, K_e did not vary with either initial concentration of disulfide or concentration of sulfuric acid. The value of K_e was 0.27 ± 0.03.

Equilibrium constants have been determined for the disproportionation of other unsymmetrical disulfides by several groups of workers.[9-11] The value of K_e of 0.27 which we find for 1 is in good accord with the data found for other systems which indicate that K_e is normally within a factor of 2 of the statistically predicted value of 0.25.[9,10]

Kinetics of the Disproportionation of 1. Experiments at different considerations of added strong acid (H_2SO_4) showed that the disproportionation of 1 was definitely acid catalyzed under our reaction conditions. The exact nature of the dependence on acid concentration will be considered later. In all runs there was a short (5–15 min), but definitely noticeable, induction period (see Figure 1) before the disproportionation began. The length of this induction period was shorter the higher the strong acid concentration (and faster the subsequent rate of disproportionation).

Once the induction period was over the kinetic data for the disproportionation gave a reasonably good fit to what would be expected for a reversible, second-order reaction of the type

$$2A \underset{k'}{\overset{k}{\rightleftharpoons}} B + C$$

A = $PhCH_2SSC_6H_4CH_3$; B = $(PhCH_2S)_2$; C = $(CH_3C_6H_4S)_2$

Frost and Pearson[12] give the following kinetic expression for such a reaction

$$\ln\left[\frac{x(a - 2x_e) + ax_e}{a(x_e - x)}\right] = k\left[\frac{2a(a - x_e)}{x_e}\right]t \qquad (8)$$

where a = initial concentration of A (1 in this case), x = moles of A per unit volume that have disproportionated in time t, x_e = moles of A per unit volume that have disproportionated when final equilibrium is reached, and the equilibrium constant for the reaction, K_e, is defined as

$$\frac{k}{k'} = K_e = \frac{(x_e/2)^2}{(a - x_e)^2}$$

In the present case if we let λ_A = magnitude of the integral for the methylene proton peak in $PhCH_2SSC_6H_4CH_3$ and λ_B = magnitude of the integral for the methylene proton peak in $(PhCH_2S)_2$ and λ_A^∞ and λ_B^∞ represent the magnitude of these same integrals once equilibrium is reached, then

$$x = a\left[\frac{\lambda_B}{\lambda_A + \lambda_B}\right] \text{ and } x_e = a\left[\frac{\lambda_B^\infty}{\lambda_B^\infty + \lambda_A^\infty}\right]$$

If we now define two new quantities

$$y = \frac{\lambda_B}{\lambda_A + \lambda_B} \text{ and } y_e = \frac{\lambda_B^\infty}{\lambda_B^\infty + \lambda_A^\infty}$$

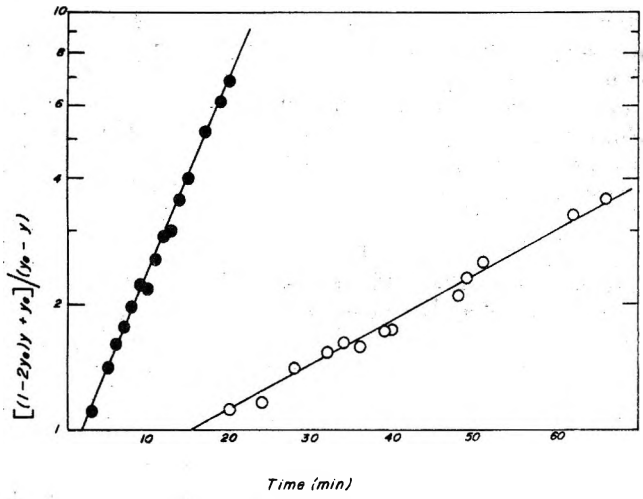


Figure 3. Effect of added *n*-butyl sulfide on the kinetics of the disproportionation of **1**. Data plotted according to eq 9. Both runs in acetic acid–0.56 *M* H_2O as solvent with 0.05 *M* H_2SO_4 and an initial concentration of **1** of 0.30 *M*. ●, 1 × 10^{-4} *M* *n*-Bu_2S added; ○, no added sulfide.

appropriate substitution in eq 8 gives eq 9, which should govern the change in the relative intensity of the two NMR methylene peaks with time, if the disproportionation of **1** does follow reversible, second-order kinetics under our reaction conditions.

$$\ln\left[\frac{(1 - 2y_e)y + y_e}{y_e - y}\right] = k\left[\frac{a}{K_e^{1/2}}\right]t \qquad (9)$$

Figure 1 shows the kinetic data for two runs, both at 0.10 *M* H_2SO_4 but involving different initial concentrations of **1**, plotted according to eq 9. Both plots are satisfactorily linear. In accord with the requirements of eq 9 a decrease in the initial concentration of **1** does appear to lead to a proportional decrease in the slope of the plot of the data vs. time. Table I summarizes the values of the rate constant, k, for the various acid and disulfide concentrations, as estimated from the slopes of plots of the data according to eq 9 and the relationship, slope = $k(a/K_e^{1/2})$.

From Table I one can see that k increases markedly with increasing concentration of sulfuric acid. A plot of log k vs. $-H_0$, the Hammett acidity function for these solutions,[13] is linear with a slope of about 0.8.

Effect of Added Mercaptan. Addition of very small concentrations of either *p*-toluenethiol or α-toluenethiol to the reaction solution led to a very marked increase in the length of the induction period observed at the start of the disproportionation. This can be seen from Figure 2, which shows a plot of the rate data for two otherwise identical runs, but to one of which was added initially 3.6 × 10^{-4} *M* *p*-toluenethiol. The run with the added thiol exhibits an induction period of almost 100 min before the disproportionation of **1** starts to proceed at a significant rate. This is in contrast to the induction period of only 5 min observed in the absence of added mercaptan. However, once the induction period is over the rate of disproportionation in the run with added mercaptan is identical, within experimental error, with the rate found in the absence of added thiol. Experiments in which the concentration of added thiol was varied showed that the length of the induction period was proportional to the amount of thiol added; thus, addition of 7.2 × 10^{-4} *M* *p*-$CH_3C_6H_4SH$ under the reaction conditions of Figure 2 gave an induction period of 195 min. Other experiments showed that a given mercaptan concentration the length of the induction period was the same with added $C_6H_5CH_2SH$ as with *p*-toluenethiol.

Table I
Kinetics of the Disproportionation of Benzyl *p*-Tolyl Disulfide in Acetic Acid–1% Water at 70°

$[ArSSR]_0$, *M*	$[H_2SO_4]$, *M*	$k \times 10^3$, M^{-1} sec^{-1} [a]
0.30	0.20	2.6
0.20	0.20	2.7
0.30	0.15	2.0
	0.10	1.2
0.20	0.10	1.1
0.30	0.05	0.69

[a] Evaluated from the slope of plots of the data for each individual run according to eq 9, using the relationship k = (slope × $K_e^{1/2}$)/$[ArSSR]_0$.

Table II
Rate of Disproportionation of Benzyl *p*-Tolyl Disulfide in the Presence of Added *n*-Butyl Sulfide[a]

$[ArSSR]_0$, *M*	$[H_2SO_4]$, *M*	$[n\text{-}Bu_2S] \times 10^4$, *M*	$k \times 10^3$, M^{-1} sec^{-1} [b]
0.30	0.05	1.00	3.1
	0.15	1.00	13.0
		0.50	7.5

[a] All data for acetic acid–1% water as solvent at 70°. [b] Evaluated from the slope of plots of the data for each individual run according to eq 9, using the relationship k = (slope × $K_e^{1/2}$)/$[ArSSR]_0$.

The experiments so far discussed were all carried out without initial degassing of the reaction solution. For solutions with no added mercaptan careful degassing of the solution had no significant effect on either the length of the short induction period or on the measured rate of disproportionation. In contrast, in runs with added mercaptan initial degassing of the solution led to a pronounced increase in the length of the induction period. For example, for the run in Figure 2 the induction period was increased from 100 to 245 min. The rate of disproportionation once the induction period was over, however, was the same as in the absence of degassing.

Effect of Added *n*-Butyl Sulfide. The addition of very small amounts (10^{-4} *M*) of *n*-butyl sulfide led to a very marked increase in the rate of disproportionation of **1**. This is evident from Figure 3, which shows the rate data for two runs, both at 0.05 *M* H_2SO_4 and 0.3 *M* **1**, one without added sulfide and the other containing 1 × 10^{-4} *M* *n*-butyl sulfide. From Figure 3 it appears that the rate data for the sulfide-catalyzed reaction give a satisfactorily linear plot vs. time when plotted according to eq 9, suggesting that the sulfide-catalyzed reaction is apparently also second order in disulfide. Experimental second-order rate constants for the different runs with added sulfide are shown in Table II. It is evident that this reaction, like the simple disproportionation, is subject to acid catalysis. From the very limited data it also appears that the rate increases with increasing sulfide concentration in an essentially linear manner.

Initial addition of mercaptan also leads to an induction period with the sulfide-catalyzed disproportionation, although the length of this induction period is much shorter than that caused by addition of the same amount of mercaptan to the ordinary disproportionation. Thus addition of either 3.6 × 10^{-4} *M* *p*-toluenethiol or $C_6H_5CH_2SH$ to an undegassed solution containing 1 × 10^{-4} *M* *n*-Bu_2S, 0.3 *M* **1**, and 0.15 *M* H_2SO_4 led to an induction period of about 10 min before disproportionation commenced instead of the

100-min period observed (Figure 2) under these conditions in the absence of sulfide. As in the other cases the rate after the induction period was over was identical with that observed in the corresponding run without added mercaptan.

Discussion

The important experimental observations regarding the disproportionation of 1 under the present reaction conditions are as follows. First, the kinetics of the approach to equilibrium show a quite good fit to what would be expected for a reversible reaction which is second order in disulfide. Second, the reaction is subject to marked acid catalysis. Third, the reaction can also be strongly catalyzed by the addition of small amounts of an *n*-alkyl sulfide. (This sulfide-catalyzed disproportionation is also acid catalyzed.) Finally, the disproportionation can be effectively completely inhibited for significant periods of time by the addition of very small amounts of either *p*-toluenethiol or benzyl mercaptan.

The inhibition by added mercaptans (Figure 2) is reminiscent of what one observes[14] for the inhibition of a free-radical chain reaction where the inhibitor suppresses the chain reaction by intercepting the chain-carrying radicals and is thereby slowly consumed in the process, so that after a certain period when the inhibitor has been completely used up the reaction commences at its normal uninhibited rate. However, when one examines this particular reaction system, it is not possible to propose any reasonable free-radical chain sequence for the disproportionation where added mercaptan could act as an inhibitor. Specifically, the only likely reactions of either thiol with a free radical are the hydrogen-atom transfers shown in eq 10, and any thiol

$$R\cdot' + RSH \longrightarrow R'H + RS\cdot \quad (10a)$$

$$R\cdot' + ArSH \longrightarrow R'H + ArS\cdot \quad (10b)$$

radicals formed in this fashion should promote, not inhibit, the disproportionation of 1 via the following reactions.

$$RS\cdot + RSSAr \longrightarrow RSSR + ArS\cdot \quad (11a)$$

$$ArS\cdot + RSSAr \longrightarrow ArSSAr + RS\cdot \quad (11b)$$

Although the inhibition by mercaptans can thus not be explained by a free-radical mechanism for the disproportionation, it could be explained by invoking a chain-type mechanism involving *ionic* intermediates where added thiol concentrations in excess of a certain value are sufficient to suppress the chain reaction almost completely. Furthermore, such a mechanism seems both a reasonable and a realistic possibility for the disproportionation of 1 under our reaction conditions. The particular mechanism that would seem to fit the data best is shown in Chart I. In this mechanism the chain-propagation steps are eq 15 and 16, which involve nucleophilic displacements by 1 on ions **2** and **3**. The steady-state concentration of **2** and **3** will be governed by the equilibria shown as eq 13 and 14. Under normal circumstances, i.e., no added mercaptan, ArSH and RSH will be present only at the *same very low* equilibrium concentration as **2** and **3**. Addition of mercaptan to a level much higher than this very low, normal, equilibrium concentration will, of course, drastically decrease the concentration of **2** (or **3**) present at equilibrium and will correspondingly reduce the rate of chain propagation, thereby leading to marked inhibition of the disproportionation.

Since inhibition of the disproportionation by added thiols in the fashion shown in Chart I would not result in any significant net consumption of the added thiol, to explain the observed (Figure 2) cessation of that inhibition after a certain time period one must assume that under our reaction conditions there are one or more side reactions that consume mercaptan irreversibly. Reasonable possibilities for such reactions exist and will be discussed later. However, let us first see if the mechanism shown in Chart I is consistent with the kinetics observed for the disproportionation in the absence of added mercaptan.

Chart I
Mechanism of the Acid-Catalyzed Disproportionation of an Unsymmetrical Disulfide

$$ArSSR + H^+ \rightleftharpoons ArS^+SR \rightleftharpoons ArSS^+R \quad (12)$$
(H on the S adjacent to Ar)

$$ArSSR + ArS^+SR \rightleftharpoons ArS^+SSR + ArSH \quad (13)$$
(H on the S adjacent to Ar; **2**)

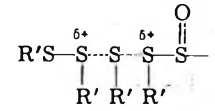
$$ArSSR + ArS^+SR \rightleftharpoons RSS^+SAr + RSH \quad (14)$$
(H on the S adjacent to Ar; **3**)

chain-propagating steps:

$$ArSSR + RSS^+SAr \rightleftharpoons ArS^+SSR + ArSSAr \quad (15)$$
(**3** → **2**)

$$ArSSR + ArS^+SSR \rightleftharpoons ArS^+SSR + RSSR \quad (16)$$
(**2** → **3**)

Besides eq 15 and 16 there are 22 additional possible reactions involving disulfides (ArSSR, RSSR, and ArSSAr) and the different possible dithiosulfonium ions (**2**, **3**, and four other –S–S$^+$–S– cations). Some of these do not lead to conversion of one disulfide to another; others do. Unless some simplification is made the complete array of reactions is too complex to analyze kinetically in a straightforward manner. Fortunately, for this particular system, one significant simplification appears justified based on certain earlier results. *p*-Tolyl disulfide and benzyl disulfide have been found[8] to exhibit closely similar reactivity in the disulfide–sulfinic acid reaction. This fact and the fact that the rate-determining transition state in that reaction has the structure



suggest that for all of the different possible displacements by disulfides on dithiosulfonium ions in the disproportionation of **1**, i.e.

$$-S-S + S-\overset{+}{S}-S- \longrightarrow -S-\overset{+}{S}-S + S-S- \quad (17)$$

the rate constants may be about the same, regardless of which particular sulfurs in eq 17 bear a *p*-tolyl group and which a benzyl group.

If we also assume that the equilibrium constants for the formation of the various dithiosulfonium ions from disulfides (eq 12–14 and analogous equations) are about the same for all the possible cations, then, to a reasonable first approximation, the mechanism in Chart I can be simplified for kinetic purposes to the following (eq 18–20)

$$D + H^+ \overset{K_1}{\rightleftharpoons} DH^+ \quad (18)$$

$$D + DH^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} I^+ + T\text{–}SH \quad (19)$$

$$D + I^+ \xrightarrow{k_3} D' + I^+ \quad (20)$$

where D = disulfide (ArSSR, RSSR, or ArSSAr), DH^+ = protonated disulfide, I^+ = **2**, **3**, and the other dithiosulfonium ions, and TSH = thiol.

For this reaction scheme the rate of interconversion of disulfides is

$$\text{Rate} = k_3[I^+][D]$$

From the stoichiometry of the scheme, unless mercaptan is deliberately added, $[I^+] = [TSH]$. If we assume a steady state in $[I^+]$, this leads to

$$[I^+] = \left[\frac{K_1 k_2}{k_{-2}}\right]^{1/2}[D]^{1/2}[DH^+]^{1/2} = \left[\frac{K_1 k_2}{k_{-2}}\right]^{1/2} h_0^{1/2}[D]$$

and to the following predicted rate expression.

$$\text{Rate} = k_3\left[\frac{K_1 k_2}{k_{-2}}\right]^{1/2} h_0^{1/2}[D]^2 \quad (21)$$

Thus, provided our assumptions are reasonably valid, the disproportionation of **1** should follow kinetics which are second order in disulfide concentration, as indeed observed. The dependence of rate on acidity is predicted to follow $h_0^{1/2}$. Because of the difficulty in defining h_0 accurately for different types of substrates in strongly acid media, one cannot really say whether the observed dependence of rate on acidity is consistent with such a half-power dependence. However, it does appear that the observed increase in rate with acid concentration is somewhat less pronounced than that found[15] for certain other acid-catalyzed reactions involving sulfur substrates in this same medium where the reaction rate would be expected to show a first-order dependence on h_0. Therefore the experimental data are certainly not inconsistent with the predicted dependence of rate on acidity.

The inhibition of the disproportionation by added thiols is, of course, explained by their effect on the equilibrium shown as eq 19.

In the experiments with added thiol the marked increase in the length of the induction period upon degassing suggests that air oxidation of mercaptan to disulfide is one of the important side reactions normally leading to consumption of added thiol and eventual termination of the induction period. Another likely route for consumption of mercaptan would be via its reaction with the solvent, acetic acid, to give a thiol ester. While we are not certain what is the origin of the short induction periods that are observed in the absence of added thiol, the high concentrations of **1** employed (0.2–0.3 *M*), the very low concentrations of thiol ($\sim 3 \times 10^{-4}$ *M*) sufficient to give quite prolonged inhibition, and the short length of those induction periods, all make it attractive to suggest that they are due to the presence of very small amounts of a thiol impurity in the starting disulfide.

The catalysis of the disproportionation of **1** by added *n*-butyl sulfide and a suggested mechanism for that catalysis remain to be discussed.

The mechanism shown in Chart II represents an explanation for the catalysis by added *n*-Bu_2S that seems plausible based on other experience.[8,15,16] From previous studies[8] we know that *n*-Bu_2S should be a much better nucleophile toward sulfur than is **1**. From the work of Smallcombe and Caserio[16] we know that the equilibrium constant for the reaction

$$MeS\overset{+}{S}(Me)\text{–}SMe + Me_2S \rightleftharpoons Me_2\overset{+}{S}SMe + MeSSMe$$

is greater than 10^3. As a consequence the equilibrium constants for eq 22 and 23 should be much more favorable than those for eq 13 and 14. Because of this the steady-state concentration of **4** and **5**, and therefore of mercaptans RSH and ArSH, should be considerably larger than the steady-state concentration of mercaptans in the mechanism in Chart I. As a result the length of the induction period caused by a given concentration of added mercaptan should be considerably shorter for the sulfide-catalyzed reaction than it is for the ordinary disproportionation, as is indeed observed. The di-*n*-butylthioalkylsulfonium ions **4** and **5** should be able to give rise to an ionic chain-type disproportionation of **1** in the manner shown in eq 24 and 25.

What sort of kinetic behavior would be expected for the mechanism in Chart II? If, as in the earlier treatment of the ordinary disproportionation, we assume that the reactivity of various species is effectively independent of whether one has a tolyl or a benzyl group attached to sulfur, then, for kinetic purposes, we can approximate the mechanism in Chart II by the following

$$D + H^+ \overset{K_1}{\rightleftharpoons} DH^+$$

$$Bu_2S + DH^+ \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} Z^+ + TSH$$

$$Z^+ + D \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} I^+ + Bu_2S \xrightarrow{k_c} Z^+ + D'$$

where Z^+ = **4** or **5**, and the other symbols have the same meaning as in eq 18–20. If we assume a steady state in $[Z^+]$ and $[I^+]$, and that, unless mercaptan is deliberately added, $[Z^+] \simeq [TSH]$, this leads to the following predicted rate expression.

$$\text{Rate} = k_b\left[\frac{k_c}{k_c + k_{-b}}\right]\left[\frac{k_a}{k_{-a}}\right]^{1/2} K_1^{1/2} h_0^{1/2}[Bu_2S]^{1/2}[D]^{3/2} \quad (26)$$

Chart II
Possible Mechanism for *n*-Butyl Sulfide Catalysis of the Disproportionation of 1

$$ArSSR + H^+ \rightleftharpoons ArS\overset{+}{S}(H)R \rightleftharpoons Ar\overset{+}{S}(H)SR \quad (12)$$

$$n\text{-}Bu_2S + ArS\overset{+}{S}(H)R \rightleftharpoons n\text{-}Bu_2\overset{+}{S}SAr + RSH \quad (22)$$

4

$$n\text{-}Bu_2S + Ar\overset{+}{S}(H)SR \rightleftharpoons n\text{-}Bu_2\overset{+}{S}SR + ArSH \quad (23)$$

5

chain-propagation steps

$$\mathbf{4} + ArSSR \rightleftharpoons n\text{-}Bu_2S + ArS\overset{+}{S}(Ar)SR \rightleftharpoons ArSSAr + \mathbf{5} \quad (24)$$

$$\mathbf{5} + ArSSR \rightleftharpoons n\text{-}Bu_2S + RS\overset{+}{S}(R)SAr \rightleftharpoons RSSR + \mathbf{4} \quad (25)$$

Equation 26 predicts that the rate should depend on the 3/2 power of disulfide concentration rather than the second power as in the simple disproportionation. However, the experimental data (Figure 3) still seem to plot just as well in accord with eq 9 as did those for the simple disproportionation. We do not know, though, whether an actual 3/2 power dependence on disulfide concentration would result in enough deviation from linearity in a plot of the data according to eq 9 for the deviation to be readily apparent. While we had time in the present study to make only a very limited investigation of the dependence of the rate on the concentration of added sulfide, this seems to be more pronounced than the half-power dependence required by eq 26.

Although the fit of the experimental data to the predictions of eq 26 does not therefore seem as good as one would like, no plausible alternative mechanism to explain the catalysis by the added sulfide is readily apparent. One possible source of part of the difficulty may simply be that the simplifying assumptions made in order to reduce the kinetic scheme to one of manageable complexity may not be entirely valid for the sulfide-catalyzed reaction. In any event we feel that the mechanism in Chart II still offers at present the best working hypothesis to explain the catalysis observed with added *n*-butyl sulfide.

Experimental Section

Preparation of Benzyl *p*-Tolyl Disulfide. The method of Harpp et al.[17] was employed. A solution of 3.80 g (0.014 mol) of *N*-(*p*-tolylthio)phthalimide and 1.74 g (0.014 mol) of distilled α-toluenethiol in 70 ml of dry benzene was refluxed under nitrogen for 72 hr. The solution was filtered to remove crystalline phthalimide and the benzene solvent was removed under reduced pressure. The residue of crude benzyl *p*-tolyl disulfide was recrystallized twice at low temperature from a small amount of ethanol and then once from ligroin. The purified disulfide melted at 33° (lit.[8] mp 33–34°), yield 3.35 g (97%).

Purification of Solvents and Other Reagents. Glacial acetic acid was purified by refluxing 1 l. of commercial glacial acetic acid with 100 g of acetyl borate for 36 hr. The acetic acid was then slowly distilled off, and the fraction boiling at 117–117.5° was collected and retained. *p*-Toluenethiol was purified by recrystallization from ethanol, mp 44°. α-Toluenethiol was purified by distillation under reduced pressure, bp 144.5° (105 mmHg). *n*-Butyl sulfide was fractionally distilled before use.

Procedure for Kinetic Runs. The required amount of benzyl *p*-tolyl disulfide (1) was weighed directly into a small volumetric flask and then dissolved in a small amount of acetic acid–1% H_2O. The proper amount of a stock solution of sulfuric acid in the same solvent was then added by pipet. In those runs containing added thiol or *n*-butyl sulfide the desired amounts of stock solutions of these reagents in acetic acid–1% water were also added at this point. The entire solution was then made up to volume with additional acetic acid–1% water, and a portion of the final solution was placed in an nmr tube which was then tightly capped. The NMR tube was then placed in the thermostatted (70°) probe of a Jeol Minimar 100 NMR spectrometer. Two or three minutes were allowed for the tube to come to thermal equilibrium and for the phase and position adjustment of the spectrum. The region where the methylene protons of 1 (δ 3.83 ppm) and benzyl disulfide (δ 3.48 ppm) absorb was integrated rapidly two to four times (this required a maximum of 30 sec) at given time intervals. The relative areas of the two methylene proton singlets were used to determine the relative concentrations of 1 and benzyl disulfide at any given time. To determine the equilibrium concentration of the two disulfides the tube was removed from the probe and allowed to stand in a 70° constant-temperature bath for an additional 2 days. Measurements of the relative areas of the two NMR peaks were then made at 24 and 48 hr after the initiation of the reaction. There was no significant change in the relative peak areas during the second 24 hr.

Independent experiments showed that the presence of added α-toluenethiol, *p*-toluenethiol, and *n*-butyl sulfide in the concentrations used did not result in any signal in the NMR region being integrated that would interfere with the accurate determination of the disulfide rates by the NMR procedure. The NMR spectra of **1**, benzyl disulfide, and *p*-tolyl disulfide were measured independently in acetic acid–1% H_2O and found to agree with those previously reported.[8]

The procedures so far described applied to those runs in which no special precautions were taken to exclude oxygen from the reaction solution. The procedure for those runs in which oxygen was excluded differed from this in the following way. First, small portions of all the necessary stock solutions were independently degassed and after the final degassing pure nitrogen was admitted to the flask containing the degassed solution, the stopcock connecting it to the vacuum system was closed, and the closed flask was transferred to a nitrogen-filled drybox. Deaerated solvent was also prepared in the same way and a solution of the disulfide and the various other reagents was prepared under nitrogen in the drybox. A portion of this solution was transferred to an NMR tube in the drybox, and the tube was tightly capped before being removed from the drybox.

Measurements showed that no appreciable disproportionation of 1 took place in any of the reaction solutions at room temperature before they were placed in the NMR probe at 70°. An experiment at 70° in which 0.3 *M* 1 was dissolved in acetic acid–1% H_2O containing only 0.005 *M* sulfuric acid showed that in the absence of a significant amount of added strong acid the rate of disproportionation of 1 in this solvent at that temperature is extremely slow. Therefore all of the measured rate of disproportionation under our reaction conditions is due to the acid-catalyzed reaction.

Registry No.—**1**, 16601-19-7; *n*-butyl sulfide, 544-40-1.

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Acid-Catalyzed Rearrangement of 2-*endo*-Phenyl-2-*exo*-hydroxyepicamphor[1]

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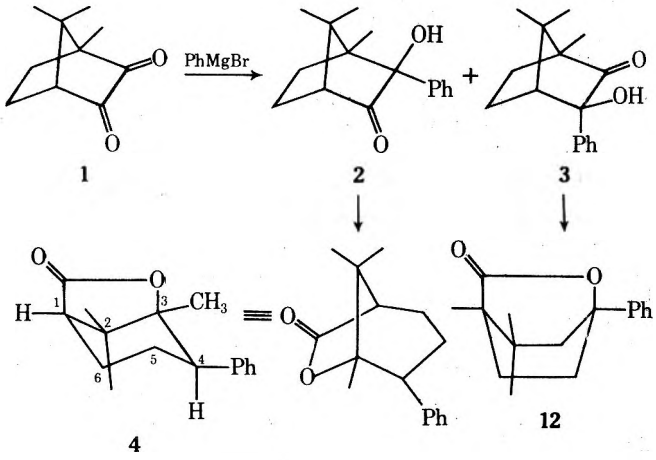
Received July 19, 1974

The molecular rearrangement of 2-*endo*-phenyl-2-*exo*-hydroxyepicamphor (2) with concentrated sulfuric acid at 0° is described. The product, isolated in yields of up to 90%, is the lactone of 3-hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylic acid (4). A possible intermediate in the rearrangement, 4-phenyl-2,2,3-trimethyl-3-cyclohexenecarboxylic acid (11), is readily converted into lactone 4 under the conditions of the rearrangement. The rearrangement of the isomeric ketol, 3-*endo*-phenyl-3-*exo*-hydroxycamphor (3), yields the lactone of 4-hydroxy-4-phenyl-1,2,2-trimethylcyclohexanecarboxylic acid (12) in low (~6%) yield.

It has been known for many years that camphorquinone (1) in cold, concentrated sulfuric acid is converted into 4-keto-2,2,3-trimethylcyclohexanecarboxylic acid.[2] Recently an extensive study of the acid-catalyzed conversion of camphor into 3,4-dimethylacetophenone has been reported by Rodig and Sysko.[3] We wish now to report that a derivative of camphor, 2-*endo*-phenyl-2-*exo*-hydroxyepicamphor (2), rearranges in concentrated sulfuric acid at 0° to the lactone of 3-hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylic acid (4).

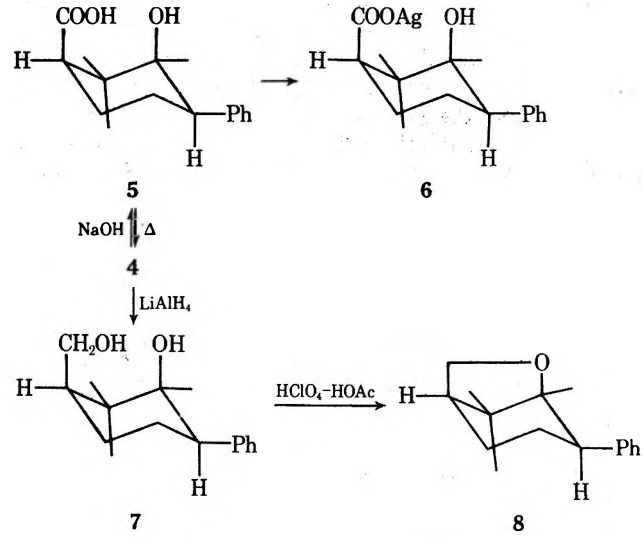
The reaction of camphorquinone with phenylmagnesium bromide afforded in good (~70%) yield and in almost equal proportions the isomeric ketols 2 and 3, which were readily



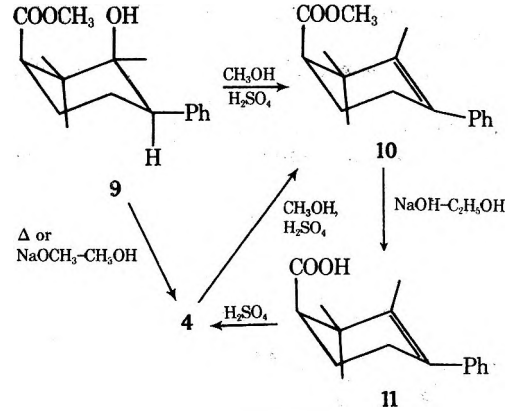
separated by fractional crystallization from methanol. To the less soluble isomer Gripenberg[4] assigned structure 2. When ketol 2 was treated with H_2SO_4 at 0° for 30 min, lactone 4 was isolated in yields of up to 90%. The lactone exhibited carbonyl absorption in the infrared at 1763 cm^{-1}, characteristic of a five-membered ring.[5]

When the lactone 4 was hydrolyzed by alcoholic NaOH, the corresponding γ-hydroxy acid 5 was obtained following cautious neutralization. To provide the silver salt of acid 5 for an X-ray analysis, the method of Youngblood[6] was employed. The infrared spectrum of this salt exhibited an OH frequency at 3209 cm^{-1} and two typical, asymmetric and symmetric, stretching vibrations at 1530 and 1389 cm^{-1}.[7] X-Ray analysis[8] of the silver salt confirmed the structure shown in 6. On pyrolysis of acid 5, lactone 4 was regenerated. Reduction of either lactone 4 or acid 5 with $LiAlH_4$ gave 3-hydroxymethyl-6-phenyl-1,2,2-trimethylcyclohexanol (7) and reaction of diol 7 with perchloric in acetic acid (1:100) or with *p*-toluenesulfonyl chloride in pyridine afforded ether 8, confirming the 1,3-cis-diaxial conformation of the hydroxymethyl and hydroxy groups.

On reaction with diazomethane, acid 5 gave ester 9, methyl 3-hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecar-



boxylate, in good yield. The ester 9 afforded lactone 4 as the sole product when heated with sodium methoxide in methanol under reflux for 2 hr or under vacuum at 80° for 5 hr. When ester 9 was heated under reflux in methanol for 9 hr with a trace of H_2SO_4, the products were lactone 4 and the unsaturated ester 10 in a ratio of 2.7 to 1. When lactone 4 was treated under similar conditions, but for a period of 7 days, the reaction mixture contained starting material (6%), ester 10 (90%), and an unidentified compound. Ester 10 was then converted with alcoholic alkali into the corre-

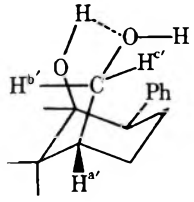


sponding acid 11 which yielded the lactone 4 under the conditions employed for rearrangement of ketol 2. It is interesting that under none of the alkaline conditions employed was there evidence of epimerization of the carbomethoxyl group from axial to the more stable equatorial geometry. In the case of the hydroxy ester 9 it must be concluded that a competitive reaction, the formation of the tertiary alkoxide which is followed by concommitant cycli-

zation and expulsion of methoxide ion to regenerate lactone **4**, is fast relative to the ionization of the α-methinyl hydrogen.

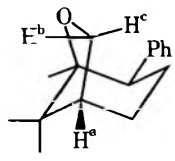
The proton nmr spectra were consistent with the structures postulated. For lactone **4**, there were three methyl singlets at δ 0.92, 1.09, and 1.19; a multiplet (4 H) centered at approximately δ 1.86; an ill-defined doubled (1 H) at δ 2.22 (J = 2.7 Hz); a doublet of doublets (1 H) at δ 2.95; and the aromatic protons at δ 7.2. The signal at δ 2.95 has been assigned to the benzyl (C_4) proton. The doublet of doublets with coupling constants J = 11.0 Hz between the C_4-benzyl proton and the C_5-axial proton, as well as the value J = 5.0 Hz between the C_4 proton and the C_5-equatorial proton, confirms the geometry of the benzyl proton as axial[9] and the aromatic ring as equatorial. The singlet at δ 2.22 has been assigned to the C_1 proton which is adjacent (α) to the carbonyl function. This signal is sharper than that of the benzyl proton, an observation which suggests that the C_1 proton occupies the equatorial position.

The nmr data for the δ 3.5–4.5 region of compounds **7** and **8** are summarized below. The protons $H^{b'}$, $H^{b'}$, and $H^{c'}$



7

$H^{b'}$, δ 4.42; $H^{c'}$, δ 4.00
$J_{b',c'}$ = 11 Hz
$J_{a'b'(c')}$ = 5.2 Hz
$J_{a'c'(b')}$ = 3.3 Hz



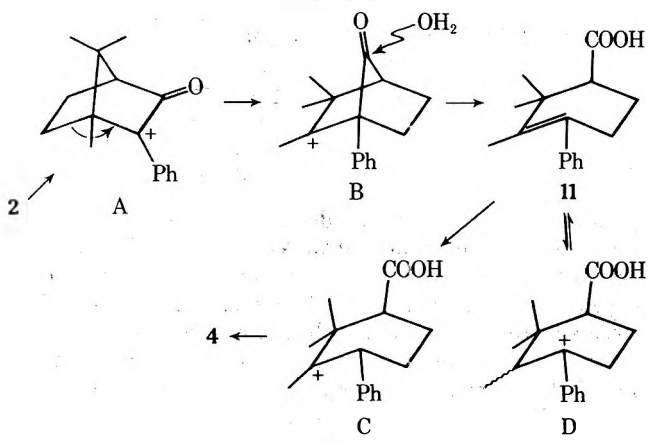
8

θ_{ab} = 18°; $\theta_{ac} \approx$ 90°
H^b, δ 4.02; H^c, δ 3.77
$J_{b,c}$ = 7.5 Hz
$J_{a,b}$ = 4.5 Hz
$J_{ac} \simeq$ 0 Hz

appear to be doublets of doublets, while H^c has only doublet character since the dihedral angle between it and H^a is approximately 90°.[10] The presence of different chemical shifts for protons $H^{b'}$ and $H^{c'}$ is evidence for a strong hydrogen bond between the two hydroxyl groups of **7** which prevents freedom of rotation of the hydroxymethyl group. The structure of **11** has been established by the proton nmr trace of the corresponding methyl ester **10**. A significant feature of the spectrum is the three-proton absorption at δ 1.50 which has been assigned to the C_3-olefinic methyl group. This methyl group is coupled with the two C_5 protons (the homoallylic position) with small coupling constants.

A route for the molecular rearrangement of 2-*endo*-phenyl-2-*exo*-hydroxyepicamphor (**2**) is suggested in Scheme I.

Scheme I



Protonation of the carbinol provides the carbonium ion A which undergoes a Wagner–Meerwein rearrangement to give B. Attack of water at the carbonyl carbon of B accompanied by a concerted collapse of the C_1–C_7 σ bond yields the unsaturated acid **11**. Reprotonation of **11** provides the ions C and D and product **4** is obtained from what would appear to be the less stable carbonium ion C since high strain inherent in the boat conformation from D militates against lactonization. Formation of lactone **4** from the unsaturated acid **11** is consistent with the mechanism suggested above.

Finally, under conditions identical with those employed for the rearrangement of ketol **2**, 3-*endo*-phenyl-3-*exo*-hydroxycamphor (**3**) gave lactone **12**, but in only a 6% yield because of the strain inherent in the boat form of **12**. The major product was polymeric ester from intermolecular esterification. The infrared spectrum of **12** exhibited C–O–C stretching at 1176 and 1121 cm^{-1} and a carbonyl absorption at 1741 cm^{-1}, characteristic of six-membered lactones.[5] In the nmr trace, there were three methyl singlets at δ 0.84, 1.05, and 1.16; a multiplet (5 H) centered at δ 7.25; and no absorption between δ 2.2 and 7.0.

Experimental Section

Melting points and boiling points are uncorrected. Analyses are by Galbraith Laboratories, Knoxville, Tenn., or M-H-W Laboratories, Garden City, Mich. Analytical glpc analyses were performed on a Varian aerograph Series 1200 instrument; preparative glpc analyses were performed on an Aerograph Model A-700 autoprep. Nmr spectra were recorded on a Varian T-60 spectrometer and infrared spectra were obtained with Perkin-Elmer Models 137 and 237 spectrometers.

2-*endo*-Phenyl-2-*exo*-hydroxyepicamphor (2) and 3-*endo*-Phenyl-3-*exo*-hydroxycamphor (3). The method of Gripenberg[4] with the following modifications was employed. A solution of 50 g (0.30 mol) of camphorquinone (**1**) in 250 ml of dry ether was added to phenylmagnesium bromide (70.6 g, 0.45 mol, of bromobenzene and 10.2 g, 0.45 mol, of magnesium turnings) in 200 ml of ether at such a rate that slow reflux was maintained. The mixture was heated overnight under reflux; it was cooled in an ice bath and cold 10% HCl solution was added. Sufficient benzene in several portions was added to dissolve all solid material. The combined organic solutions were washed with 10% $NaHCO_3$ solution and with water and were then dried over $MgSO_4$. Benzene was removed under vacuum and the residue was dissolved in methanol (~600 ml). On cooling, a crop of 32.3 g of the crude isomer **2**, mp 184–190°, was obtained. On recrystallization from 400 ml of methanol, the yield was 28.0 g (38.2%) of ketol **2**, mp 193–194° (reported 193°). The volume of the filtrate was reduced and the residue was dissolved in hot hexane. On cooling, the yield of crude ketol **3** was 29.7 g, mp 109–113°. Recrystallization from 5:1 hexane–methanol yielded 25.5 g (34.8%) of **3**, mp 111–113° (reported 114–115°).

Lactone 4 of 3-Hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylic Acid. To 100 ml of concentrated H_2SO_4 at 0° was added in one portion 13 g (0.053 mol) of the ketol **2**. The mixture was stirred vigorously for 30 min at 0° and was poured into 1500 ml of an ice–H_2O mixture. The mixture was saturated with NaCl and extracted several times with ether. The combined ether layers were washed with saturated $NaHCO_3$ and H_2O and were then dried over magnesium sulfate. Removal of solvent afforded 10.85 g of crude product. Recrystallization from methanol–water afforded 10.7 g (92.5%) of the lactone **4**, mp 110.5–111°.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.61; H, 8.24.

Reaction of the Lactone 4 with NaOH. 3-Hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylic Acid (5) and Its Silver Salt 6. A mixture of 5.0 g (0.020 mol) of the lactone and 4 g of NaOH in 70 ml of 50% ethanol was heated under reflux for 4 hr, was cooled, and then was acidified with concentrated HCl. The aqueous mixture was saturated with NaCl and extracted with ether. The combined ether solutions were washed with H_2O and dried over magnesium sulfate. Removal of solvent afforded 5.1 g (94%) of hydroxy acid **5**, mp 89–92°. Two recrystallizations from acetone–water gave a sample, mp 93–94°. The acid was characterized as its silver salt **6**, which was prepared by the method of Youngblood.[6] To a suspension of acid **5** in water was added enough

aqueous NH_3 to dissolve the acid and to make the solution just slightly basic to litmus. An equivalent amount of $AgNO_3$ in water was added slowly with stirring. The white solid which resulted was separated by filtration and was washed with water, ethanol, and then ether. Recrystallization from 95% ethanol afforded crystals for X-ray analysis.[8]

When heated at 100–110° for 30 min under house vacuum, the acid 5 (0.50 g) gave a residue which on recrystallization from methanol–water yielded lactone 4 (0.40 g, 87%), mp 110.8–112°. A mixture melting point with an authentic sample of 4 was not depressed.

Reduction of the Lactone 4 with $LiAlH_4$. 3-Hydroxymethyl-6-phenyl-1,2,2-trimethylcyclohexanol (7). A mixture of 7.0 g (0.028 mol) of lactone 4 and 0.4 g (0.011 mol) of $LiAlH_4$ in 140 ml of dry ether afforded 4.0 g (56%) of the diol 7. Recrystallization from methanol gave the pure diol, mp 168.5–169.8°.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.13; H, 9.76.

Reduction of Hydroxy Acid 5 with $LiAlH_4$. Crude diol 7 (1 g) was obtained from 1 g of the hydroxy acid and $LiAlH_4$ in dry ether. Recrystallization from methanol–water afforded 0.7 g (74%) of the diol 7, mp 168.5–169.8°. A mixture melting point with the diol prepared in the reduction above was not depressed.

Reaction of 3-Hydroxymethyl-6-phenyl-1,2,2-trimethylcyclohexanol (7) with $HClO_4$–HOAc. Preparation of the Ether 8. A mixture of 0.4 g of the diol 7 and 20 ml of a solution of $HClO_4$ in HOAc (1:100) was stored with occasional stirring at ambient temperature for 19 hr. A standard work-up afforded 0.29 g (78%) of the ether 8, bp 95–100° (0.3 mm).

Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.25; H, 9.77.

Reaction of 3-Hydroxymethyl-6-phenyl-1,2,2-trimethylcyclohexanol (7) with *p*-Toluenesulfonyl Chloride in Pyridine. The diol (1.2 g, 0.005 mol) dissolved in 10 ml of pyridine was cooled in an ice–salt bath and a solution of 1.20 g (0.0063 mol) of *p*-toluenesulfonyl chloride in 7 ml of pyridine was added slowly. The reaction mixture was stirred at 0° for 4 hr and was then stored in a refrigerator for 2 days. The mixture was poured into ice-cooled 10% HCl solution and was extracted several times with ether. Removal of solvent afforded 0.7 g (70%) of ether 8, bp 95–100° (0.3 mm).

Methyl 4-Phenyl-2,2,3-trimethyl-3-cyclohexenecarboxylate (10). A mixture of 1.95 g of lactone 4, 75 ml of dry methanol, and 7.5 ml of concentrated H_2SO_4 was refluxed for 5 days. The reaction mixture was cooled to room temperature and was then poured into 300 ml of an ice–H_2O mixture. The aqueous mixture was extracted several times with ether and the combined ether layers were washed with 10% $NaHCO_3$ and H_2O and dried over magnesium sulfate. Removal of the solvent afforded 1.7 g of the crude oil which consisted of 90.5% of the ester 10, 5.6% of the lactone 4, and 3.9% of an unknown substance, determined by glpc on a SE-30 column at 180°. The ester 10 was purified through preparative glpc.

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.63. Found: C, 79.22; H, 8.68.

4-Phenyl-2,2,3-trimethyl-3-cyclohexenecarboxylic Acid (11). (A) Saponification of Methyl 4-Phenyl-2,2,3-trimethyl-3-cyclohexenecarboxylate (10). The mixture of 0.8 g (0.003 mol) of the ester 10 and 0.8 g of NaOH in 10 ml of 50% ethanol was refluxed for 5 hr and then cooled. A standard work-up gave 0.6 g (79%) of the unsaturated acid which on recrystallization from ethanol–water exhibited mp 163.5–165.5°.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 79.05; H, 8.25.

Reaction of 4-Phenyl-2,2,3-trimethyl-3-cyclohexenecarboxylic Acid (11) with Concentrated H_2SO_4. To 2.5 ml of concentrated H_2SO_4 at 0° was added in one portion 0.2 g of the unsaturated acid and the solution was stirred at 0° for 30 min. Work-up afforded 0.16 g (80%) of the crude lactone 4 which was contaminated with less than 2% impurity, according to a glpc analysis. Two recrystallizations from methanol–water afforded pure lactone 4, mp 110–111°. A mixture melting point with the sample obtained from the rearrangement of 2-*exo*-hydroxy-2-*endo*-phenylepicamphor was not depressed.

Methyl 3-Hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylate (9). Diazomethane was prepared by the action of NaOH on bis(*N*-methyl-*N*-nitroso)terephthalamide. To the freshly prepared diazomethane in ether was added 1.50 g (0.0057 mol) of the hydroxy acid 5 in dry ether at room temperature. The mixture was stirred for 20 min and excess diazomethane was destroyed by addition of formic acid. The ether solution was filtered, washed with 3% $NaHCO_3$ and H_2O, and was then dried. Removal of solvent afforded 1.4 g (95%) of the crude ester 9. Three recrystallizations from cold ligroine gave an analytical sample, mp 58.0–59.5°.

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.04; H, 8.89.

Attempted Epimerization of Methyl Ester 9. A mixture of the hydroxy ester 9 and $NaOCH_3$ in MeOH was heated under reflux for 2 hr. Work-up gave the lactone 4.

Pyrolysis of Methyl Ester 9. The ester was heated at 80° under house vacuum for 5 hr. The product was identified as the lactone 4 by comparison of its nmr, ir, and melting point with an authentic sample.

Reaction of Methyl Ester 9 with MeOH and H_2SO_4. A mixture of 0.5 g of the ester 9, 4 ml of CH_3OH, and 10 drops of concentrated H_2SO_4 was heated under reflux for 9 hr. Work-up gave a 1:2.7 ratio of 10 to 4 according to a glpc analysis.

Lactone 12 of 4-Hydroxy-4-phenyl-1,2,2-trimethylcyclohexanecarboxylic Acid. To 80 ml of concentrated H_2SO_4 at 0° was added in one portion 7.8 g (0.040 mol) of the ketol 3. The mixture was stirred vigorously for 30 min at 0° and poured into 1300 ml of an ice–H_2O mixture. The mixture was saturated with NaCl and extracted several times with ether. The combined ether solution was washed with saturated $NaHCO_3$ and H_2O and then was dried over magnesium sulfate. Removal of solvent afforded 6.6 g (85%) of the crude residue which was distilled under reduced pressure. The fraction, bp 143–145° (0.4 mm), was collected and crystallized from hexane. The yield was 0.50 g (6.4%) of lactone 12, mp 87.9–89°.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.67; H, 8.25.

The residue, a polymeric material, was recrystallized from acetone–water, mp >190°. An ir trace exhibited typical ester bands at 1111, 1171, and 1729 cm^{-1} and hydrolysis gave a nonuniform product.

Acknowledgment. We are grateful to Ms. Margery S. Sved for assistance in the preparation of one of the compounds described herein.

Registry No.—1, 465-29-2; 2, 35202-03-0; 3, 53684-40-5; 4, 53684-41-6; 5, 53684-42-7; 7, 53684-43-8; 8, 53684-44-9; 9, 53684-45-0; 10, 53684-46-1; 11, 32623-12-4; 12, 53684-47-2; bromobenzene, 108-86-1.

References and Notes

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Double-Bond Rearrangements of Inden-1-yl Derivatives

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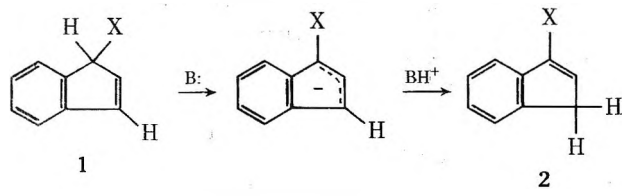
Received September 18, 1974

The rates of double-bond rearrangement of ten different inden-1-yl derivatives to the corresponding inden-3-yl derivatives have been determined in pyridine at 40°. No linear free-energy relationship has been found which fits all of the data. However, the unexpectedly high reactivities observed for many of the compounds clearly indicate the care with which they must be handled in the presence of even weakly basic amines if their isomeric integrities are to be preserved.

In connection with another investigation, we have carried out a study of the rates of pyridine promoted double-bond rearrangement of a variety of inden-1-yl derivatives **1** to the corresponding inden-3-yl derivatives **2**. Such amine



1 **2**

promoted rearrangements are well documented in the literature,[1-4] and have recently received considerable attention due to the fact that they have been shown[2] to proceed *via* a suprafacial conducted tour route for the 1,3-proton transfer. However, except for 1-deutericindene[3] and various alkyl-substituted indenes,[2,4] only very qualitative kinetic data are available and most of these have been obtained using a wide variety of bases, solvents, and reaction conditions.

For our kinetic studies, small scale nmr techniques were used to follow the course of the rearrangements. Pyridine was used simultaneously as the base and the solvent, and all of the rearrangements were examined at 39.5 ± 1.5°. The inden-1-yl derivatives examined were limited to those which were already available to us in connection with our other investigation, or which could be readily synthesized from these. However, the substituents present on these derivatives represent a variety of inductive and resonance effect behaviors. The syntheses and characterizations of each of the inden-1-yl and -3-yl derivatives encountered are described in the Experimental Section. Five of the inden-1-yl derivatives are reported here for the first time.

In all of the cases we have examined, the rearrangements of the inden-1-yl derivatives proceeded cleanly to the corresponding inden-3-yl derivatives or an equilibrium mixture, except for inden-1-ol which gave indan-1-one *via* enol–keto tautomerization of the initially formed inden-3-ol. The kinetic data obtained for the rearrangements are summarized in Table I. The average integrated first-order rate constants given for the forward processes in the rearrangements studied were calculated assuming that pseudo-first-order or reversible pseudo-first-order rate behavior would be followed.[5]

For most of the rearrangements which proceeded at convenient rates the correctness of this assumption was borne out by the fits obtained for the data. The errors shown are mean deviations of the integrated first-order rate constants calculated from at least six or seven experimental points. However, the pseudo-first-order reversible fit for the data from rearrangement of 3-deuterioindene was very poor owing to the experimental inaccuracies inherent in the fact that the rearrangement was followed by integration of an nmr absorption which only decreased by 30% overall during the course of the rearrangement. Thus, the data were treated graphically. In the case of 1-phenylindene, the rearrangement was so fast that the earliest point which could be measured indicated over 58% rearrangement and the rate constant shown is the best estimate available from several runs. Finally, for the inden-1-yl carboxylic acid, in all cases by the time an nmr spectrum of the reaction mixture could be taken only the presence of the inden-3-yl derivative could be observed. Thus, the rate constant given in this case is only a minimum value.

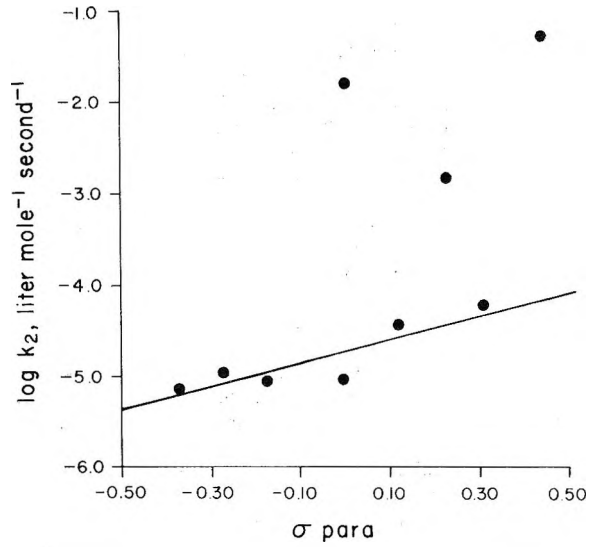


Figure 1. Plot of log k_2 *vs.* σ para for rearrangement of inden-1-yl derivatives in pyridine at 39.5 ± 1.5°.

Table I also gives the values for the calculated second-order rate constants for the rearrangements studied. No error is given for these since they include the errors in pyridine concentrations. These errors in concentration may be as great as ±5% owing to the problems inherent in measuring the very small volumes of the reaction mixtures used.

It is seen that for the inden-1-yl derivatives examined the rates for rearrangement spanned a range of at least four powers of ten. The high reactivities for even the acetate, *p*-nitrobenzoate, and 3,5-dinitrobenzoate derivatives clearly point out the care with which an experimentalist must handle inden-1-yl derivatives even in the presence of weak bases such as pyridine if problems due to isomerization to the corresponding inden-3-yl derivatives are not to be encountered.

Attempts to find a linear free-energy relationship which would give a good fit for all of the data were unsuccessful, as might have been expected and as is shown by the σ para plot given in Figure 1. Various other treatments involving use of different types of σ values in the Hammett relation-

Table I
Rates of Double-Bond Rearrangement of Some Inden-1-yl Derivatives in Pyridine at 39.5 ± 1.5°

Substituent	[Indene], M	[Pyridine], M	% conversion at equilibrium	$10^4 k_1$, sec^{-1}	$10^5 k_2$, $M^{-1} sec^{-1}$ [a]
-OH	3.6	6.7	99 ± 1[b]	0.050 ± 0.001	0.075
	3.3	7.2	99 ± 1[b]	0.052 ± 0.002	0.072
	3.3	7.2	99 ± 1[b]	0.051 ± 0.004	0.071
$-CH_3$	3.7	6.5	97 ± 2	0.053 ± 0.002	0.082
	3.5	6.9	99 ± 1[c]	0.053 ± 0.002	0.077
	3.3	7.1	99 ± 1[c]	0.074 ± 0.004	0.10
-H[d]	3.9	6.9	63 ± 5	0.059[e]	0.086
	3.2	8.0	60 ± 5	0.068[e]	0.085
$-OCH_3$	3.0	7.1	94 ± 2	0.080 ± 0.010	0.11
	2.7	7.9	94 ± 2	0.074 ± 0.008	0.094
	3.3	6.6	91 ± 2	0.074 ± 0.008	0.11
$-CH_2OH$	3.6	6.1	94 ± 1	0.22 ± 0.01	0.36
	3.4	6.4	94 ± 1	0.23 ± 0.02	0.36
	3.3	6.6	94 ± 1	0.19 ± 0.01	0.29
	2.8	7.5	91 ± 1	0.22 ± 0.01	0.29
-OAc	2.4	7.4	96 ± 1	0.39 ± 0.01	0.53
	2.3	7.6	97 ± 1	0.43 ± 0.03	0.57
	2.7	6.8	96 ± 1	0.34 ± 0.03	0.50
	2.5	7.2	96 ± 1	0.40 ± 0.02	0.56
-OPNB	1.1	8.8	95 ± 5	1.8 ± 0.1	2.0
	1.2	8.3	95 ± 5	1.4 ± 0.1	1.7
-ODNB	0.61	10	95 ± 5	3.5 ± 0.2	3.5
	0.59	10	95 ± 5	4.5 ± 0.1	4.5
-Cl	2.3	8.3	99 ± 1[c]	12 ± 1	14
	2.4	8.2	99 ± 1[c]	8.6 ± 1	10
	2.2	9.0	99 ± 1[c]	14 ± 1	16
$-C_6H_5$	1.8	8.2	99 ± 1[c]	120[f]	150
$-CO_2H$	1.6	9.5	99 ± 1[c]	> 460	> 480

[a] $10^4 k_1$ divided by [pyridine]. [b] No starting material observed under conditions where 1% would have been clearly observed. [c] Less than 1% starting material observed. [d] Starting material is 3-deuterioindene. [e] Determined graphically. [f] Determined graphically with points from several different runs being plotted together.

ship as well as steric effects were also considered and gave even poorer fits. That a simple Hammett type correlation for the 1-substituted indene isomerization data should not be expected is apparent from consideration of several factors. The rate constants we measured are for formation of isomerized product and not for proton abstraction at the 1 position. These should not be identical with varying 1 substituents owing to the likelihood of invisible proton readdition to the 1 position, and also would not be expected to have a constant ratio. Furthermore, not only inductive and conjugative effects but also the differing steric and dipolar field effect interactions of the 1 substituents should greatly affect the stabilities of the respective activated complexes for 1-proton abstraction.

For completeness, we have also made a brief examination of the literature for evidence regarding the propensities for rearrangement of our and other inden-1-yl to inden-3-yl derivatives in the presence of bases. A number of examples of the rearrangements of 1-alkylindenes are available in the literature, as mentioned earlier. In accord with the high reactivity we observed for 1-phenylindene, Kende and Bogard[6] reported that this material in deuteriochloroform solution at room temperature rapidly isomerized to 3-phenylindene upon the addition of one drop of triethylamine. Also, Meth-Cohn and Gronowitz[7] reported the instantaneous rearrangement of inden-1-yl carboxylic acid upon similar treatment. Finally, Kerber and Hodos[8] observed that 1-nitroindene was rapidly isomerized to 3-nitroindene in deuteriochloroform solution at room temperature even in the absence of added base.

Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were obtained on a Varian A-60A instrument with chemical shifts measured in parts per million (δ) downfield from TMS internal or external standard. Mass spectra were run on a CEC Model 21-104 single focusing instrument by Mr. J. Voth. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Indan-1-one. This was prepared in 62% yield by the procedure of Arcus and Barrett[9] through the reaction of hydrocinnamic acid (Eastman White Label) and polyphosphoric acid: bp 89–90° (0.6 mm); mp 39–40° [lit.[9] bp 120–122° (15 mm); mp 38°]; nmr (CCl_4) δ 2.5 (m, 2 H, $CH_2C{=}O$), 2.9 (m, 2 H, CH_2-arom), and 7.4 ppm (m, 4 H, **arom**).

1-Deuterioindan-1-ol. This was prepared on small scale in 50% yield by reduction of indan-1-one with lithium aluminum deuteride (Ventron, 18.7% D) and recrystallized from 1:1 ether–petroleum ether: mp 51–53° [lit.[10] mp 53–54° (for nondeuterated material)]; nmr (CCl_4) δ 2.0 (m, 2 H, CH_2CDOH), 2.7 (m, 2 H, CH_2-arom), 4.3 (bs, 1 H, **OH**), and 7.1 ppm (m, 4 H, **arom**). Nmr examination showed that this material contained less than 2% of one H on C_1 (δ 4.9 ppm).

3-Deuterioindene. A finely crushed mixture of 1.0 g (0.0074 mol) of 1-deuterioindan-1-ol and 1.3 g (0.011 mol) of anhydrous magnesium sulfate when heated to 120° at 32 mm pressure yielded 0.6 g (69%) of crude product. Redistillation through a microdistillation apparatus gave 0.5 g of pure 3-deuterioindene: bp 85–88° (35 mm); $n^{23.5}$D 1.5740 [lit.[11] bp 182 (740 mm); n^{25}D 1.5739 (for nondeuterated material)]; nmr (CCl_4) δ 3.2 (d, J = 2 Hz, 2 H, CH-CH_2), 6.3 (m, 1 H, =CH-CH_2) and 7.1 ppm (m, 4 H, **arom**); mass spectrum (70 eV) m/e (rel intensity) 118 (10), 117 (100), 116 (81), 115 (14), 63 (11), 58 (9), 39 (8). Nmr examination showed that this material contained less than 2% of one H on C_3 (δ 6.6 ppm).

Inden-1-ol. This was prepared in 33% overall yield by a modified method from that of Hock and Ernst.[12] Oxygenation of inden-

1-yllithium at −78° followed by reduction of the intermediate inden-1-yl hydroperoxide with potassium iodide in aqueous acetic acid produced the desired inden-1-ol; bp 95–96° (1.4 mm). It was recrystallized from 4:1 petroleum ether–ether to yield white plates: mp 55–56° (lit.[13] mp 47°); nmr (CCl_4) δ 3.2 (bs, 1 H, CHOH), 4.9 (bs, 1 H, CHOH), 6.2 (doublet of doublets, J = 2 and 6 Hz, 1 H, CH-CHOH), 6.5 (doublet of doublets, J = 1 and 6 Hz, 1 H, CH-arom), and 7.3 ppm (m, 4 H, **arom**); mass spectrum (70 eV) m/e (rel intensity) 132 (100), 131 (79), 115 (15), 104 (15), 103 (34), 77 (34), 51 (30), 50 (10), and 18 (20).

3-Methylindan-1-one. This was prepared in 82% yield by the method of Koelsch and coworkers[13] through the reaction of crotonic acid with benzene in the presence of aluminum chloride: bp 78–85° (1.5 mm); n^{24}D 1.5555 [lit.[13] bp 132–137° (15 mm)]; nmr (CCl_4) δ 1.3 (d, J = 7 Hz, 3 H, CH_3), 2.2 (doublet of doublets, J = 4 and 19 Hz, 1 H, CH-C=O), 2.7 (doublet of doublets, J = 7 and 19 Hz, 1 H, CH-C=O), 3.3 (m, 1 H, CH-CH_3), and 7.4 ppm (m, 4 H, **arom**).

3-Methylindan-1-ol. Reduction of 3-methylindan-1-one in ether with lithium aluminum hydride followed by recrystallization from petroleum ether gave a 61% yield of 3-methylindan-1-ol as tiny white needles: mp 70–72° (lit.[15] mp 69°); nmr (CCl_4) δ 1.3 (m, 4 H, CH-CH_3), 2.8 (m, 2 H, CH_2), 4.5 (bs, 1 H, OH), 5.2 (t, J = 8 Hz, 1 H, CH-OH), and 7.5 ppm (m, 4 H, **arom**).

1-Methylindene. This was prepared on small scale in 31% yield by the method of Bergson and Weidler[4a] through 20% sulfuric acid catalyzed dehydration of 3-methylindan-1-ol at 100°; bp 64–70° (10 mm); $n^{23.5}$D 1.5554 [lit.[14] bp 82° (15 mm); n^{20}D 1.5569]; nmr (CCl_4) δ 1.3 (d, J = 7 Hz, 3 H, CH_3), 3.4 (q, J = 7 Hz, 1 H, CH-CH_3), 6.4 (doublet of doublets, J = 2 and 5 Hz, 1 H, =CH-CH), 6.7 (doublet of doublets, J = 2 and 6 Hz, 1 H, = CH-arom), and 7.2 ppm (m, 4 H, **arom**).

In another preparation, 67.3 g (0.46 mol) of 3-methylindan-1-ol and 90 g (0.75 mol) of powdered anhydrous magnesium sulfate were heated at 140–155° for about 1 hr (18 mm). The dried distillate consisting of 1-methylindene weighed 53 g (88%).

3-Methylindene. 1-Methylindene (53 g, 0.41 mol) was refluxed with 5 ml of triethylamine for 2 hr. Distillation afforded 50 g (94%) of 3-methylindene: bp 77–79° (18 mm); n^{21}D 1.5565 [lit.[15] bp 70° (10 mm); n^{25}D 1.5595]; nmr (Et_3N) δ 1.8 (m, 3 H, CH_3), 2.8 (m, 2 H, CH_2-arom), 5.7 (m, 1 H, =CH-CH_2), and 6.9 ppm (m, 4 H, **arom**).

1-Methoxyindene. Into a 100-ml flask was added 2.0 g (0.015 mol) of inden-1-ol and 20 ml of trimethyl orthoformate. Then 3.2 g (0.032 mol) of 70% aqueous perchloric acid was added dropwise. The solution was stirred for 20 min at *ca.* 35° and then was poured into 100 ml of ice-cold saturated aqueous sodium bicarbonate. The resulting mixture was extracted with three 30-ml portions of ether. The combined ether extracts were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated by rotary vacuum evaporation. Distillation of the remaining oil afforded 1.1 g (50%) of 1-methoxyindene: bp 71–74° (3.9 mm); $n^{23.5}$D 1.5531; nmr (CCl_4) δ 3.1 (s, 3 H, OCH_3), 5.0 (bs, 1 H, CH-OCH_3), 6.4 (doublet of doublets, J = 2 and 4 Hz, 1 H, =CH-CH-OCH_3), 6.8 (d, J = 6 Hz, 1 H, =CH-arom), and 7.2 ppm (m, 4 H, **arom**); mass spectrum (70 eV) m/e (rel intensity) 147 (11), 146 (100), 145 (11), 131 (88), 115 (64), 103 (91), 77 (30), and 63 (29).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 82.04; H, 6.87.

3-Methoxyindene. 1-Methoxyindene (0.23 g, 0.0016 mol) was heated with 0.3 ml of triethylamine at 40° for 1 hr. Distillation yielded 0.17 g (74%) of 3-methoxyindene contaminated with 4% of 1-methoxyindene: bp 116–117° (20 mm); $n^{23.5}$D 1.5657 [lit.[16] bp 101–104° (15 mm)]; nmr (CCl_4) δ 3.2 (d, J = 2 Hz, 2 H, CH_2-arom), 3.8 (s, 3 H, OCH_3), 5.1 (t, J = 2 Hz, 1 H CH=CH-OMe), and 7.2 ppm (m, 4 H, **arom**).

1-Hydroxymethylindene. This was material containing 5% 3-hydroxymethylindene prepared by Friedrich and Holmstead[17] by the reaction of indenylmagnesium bromide with paraformaldehyde: bp 88–91° (0.8 mm) [lit.[18] bp 134° (10 mm)]; nmr (CCl_4) δ 3.6 (m, 4 H, $HOCH_2CH$), 6.4 (d, 1 H, J = 5 Hz, =CH-$CHCH_2OH$), 6.7 (d, 1 H, J = 5 Hz, =CH-arom) and 7.1 ppm (m, 4 H, **arom**).

3-Hydroxymethylindene. A mixture of 5.0 g (0.034 mol) of 1-hydroxymethylindene and 2 ml of cyclohexylamine in 20 ml of ether was refluxed for 10 min. The resulting mixture was washed with 5 ml of 1 *M* hydrochloric acid, dried over anhydrous magnesium sulfate, and distilled at 100–108° (1.2 mm) to produce 2.6 g (52%) of crude 3-hydroxymethylindene. Recrystallization from 20 ml of 1:1 chloroform–carbon tetrachloride afforded 2.0 g of white crystals: mp 67–69° (lit.[19] mp 68°); nmr ($CDCl_3$) δ 2.9 (bs, 1 H, OH), 3.2 (m, 2 H, CH_2), 4.5 (m, 2 H CH_2OH), 6.4 (m, 1 H, =CH-CH_2), and 7.3 ppm (m, 4 H, **arom**)

1-Acetoxyindene. A mixture of 0.74 g (0.0056 mol) of inden-1-ol and 3 ml (0.042 mol) of acetyl chloride was refluxed on a steam bath for 10 min. Distillation yielded 0.71 g (73%) of 1-acetoxyindene: bp *ca.* 85° (1 mm); n^{24}D 1.5455; nmr (CCl_4) δ 2.0 (s, 3 H, CH_3), 6.2 (m, 2 H, =CH-CH-OAc), 6.6 (d, J = 5 Hz, 1 H, =CH-arom), and 7.2 ppm (m, 4 H, **arom**).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.84; H, 5.93.

3-Acetoxyindene. A mixture of 0.42 g (2.4 mmol) of 1-acetoxyindene and 0.5 ml of triethylamine was heated at 40° for 1.5 hr. Distillation produced 0.19 g (45%) of a 95:5 mixture of the 3- and 1-acetoxyindenes: bp 78–81° (0.6 mm); $n^{23.5}$D 1.5512 [lit.[20] bp 77–85° (0.2–0.25 mm)]; nmr (CCl_4) δ 2.1 (s, 3 H, CH_3), 3.2 (d, J = 2 Hz, 2 H, CH_2), 6.3 (m, 1 H, =CH-CH_2), and 7.2 ppm (m, 4 H, **arom**).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.68; H, 5.66.

Inden-1-yl *p*-Nitrobenzoate. A mixture of 1.0 g (0.0076 mol) of inden-1-ol and 1.5 g (0.0081 mol) of recrystallized *p*-nitrobenzoyl chloride in 20 ml of pyridine at −15° was stirred intermittently over a period of 1.5 hr. The mixture was poured into 100 ml of 1 *M* hydrochloric acid and the precipitate collected was recrystallized from 2:1 pentane–chloroform to afford 1.05 g (48%) of the desired *p*-nitrobenzoate: mp 81–83°; nmr ($CDCl_3$) δ 6.5 (m, 2 H, =CH-CHOPNB), 6.9 (m, 1 H =CH-arom), 7.3 (m, 4 H, **arom**), and 8.2 ppm (m, 4 H, **arom**).

Anal. Calcd for $C_{16}H_{11}NO_4$: C, 68.36; H, 3.94. Found: C, 68.59; H, 3.96.

Inden-3-yl *p*-Nitrobenzoate. A mixture of 0.6 g (0.0021 mol) of inden-1-yl *p*-nitrobenzoate and 0.5 ml of triethylamine in 10 ml of chloroform was refluxed for 20 min. Removal of the solvent gave a solid which was recrystallized from 10 ml of 1:1 chloroform–petroleum ether to afford 0.4 g (67%) of inden-3-yl *p*-nitrobenzoate: mp 122–124° [lit.[12] mp 122°]; nmr ($CDCl_3$) δ 3.4 (d, J = 2 Hz, 2 H, CH_2), 6.5 (t, J = 2 Hz, 1 H, =CH-CH_2), 7.3 (m, 4 H, **arom**), and 8.2 ppm (m, 3 H, **arom**).

Inden-1-yl 3,5-Dinitrobenzoate. A sample of 30 ml of pyridine was cooled to −25°, and 1.7 g (0.013 mol) of inden-1-ol was added followed in portions by 3.5 g (0.015 mol) of 3,5-dinitrobenzoyl chloride. The mixture was kept at −20 to −25° for 2 hr and then poured into 150 ml of ice-cold 0.3 *M* HCl. The precipitate was collected and recrystallized from 150 ml of 1:1 chloroform–petroleum ether to yield 2.55 g of powdery beads, mp 142–145°, and 0.80 g, mp 136–141°. The overall yield was 86% and the material showed no inden-3-yl rearrangement product: nmr ($CDCl_3$) 6.5 (1 H, CH-CH-ODNB), 6.5 (bs, 1 H, CH-ODNB), 6.9 (dd, J = 2 and 6 Hz, 1 H, CH-arom), 7.3 (m, 4 H, **arom**), and 9.2 ppm (s, 3 H, **arom**).

Anal. Calcd for $C_{16}H_{10}N_2O_4$: C, 58.90; H, 3.09; N, 8.59. Found: C, 58.76; H, 3.13; N, 8.42.

Inden-3-yl 3,5-Dinitrobenzoate. Into a well stirred solution of 30 ml of pyridine and 1 g (0.0082 mol) of inden-1-ol at room temperature was added in portions 2.2 g (0.092 mol) of 3,5-dinitrobenzoyl chloride. After standing for 1 hr at room temperature, the solution was poured into ice–water and the precipitate collected was recrystallized from 1:1 chloroform–methylcyclohexane to give 0.7 g (35%) of inden-3-yl 3,5-dinitrobenzoate: mp 179–182° (lit.[12] 181°); nmr ($CDCl_3$) δ 3.6 (d, J = 2 Hz, 2 H, CH_2), 6.7 (t, J = 2 Hz, 1 H, =CH-CH_2), 7.5 (m, 4 H, **arom**) and 9.4 ppm (m, 3 H, **arom**).

Anal. Calcd for $C_{16}H_{10}N_2O_4$: C, 58.90; H, 3.09; N, 8.59. Found: C, 58.71; H, 3.26; N, 8.42.

Also obtained as a second crop from the recrystallization was 0.7 g of a mixture of the inden-1-yl and -3-yl 3,5-dinitrobenzoates, mp 131–140°.

1-Chloroindene. A mixture of 1.25 g (0.0095 mol) of inden-1-ol and 6 ml (0.083 mol) of thionyl chloride was refluxed for 30 min. Distillation of the reaction mixture produced 0.65 g (46%) of 1-chloroindene: bp 68–71° (2.7 mm); n^{24}D 1.5865; nmr (CCl_4) δ 5.1 (s, 1 H, CHCl), 6.2 (doublet of doublets, J = 2 and 6 Hz, 1 H, =CH-CHCl), 6.6 (d, J = 6 Hz, 1 H, =CH-arom), and 7.1 ppm (m, 4 H, **arom**).

Anal. Calcd for C_9H_7Cl: C, 71.78; H, 4.68. Found: C, 71.66; H, 4.65.

3-Chloroindene. A mixture of 0.65 g of 1-chloroindene and 2 ml of triethylamine was refluxed for a short period and then distilled to yield 0.35 g (54%) of 3-chloroindene: bp 78–81° (4 mm); n^{24}D 1.5817 [lit.[21] bp 109–110° (16 mm); n^{23}D 1.5808]; nmr (neat) δ 2.9 (d, J = 2 Hz, 2 H, CH_2-arom), 6.1 (t, J = 2 Hz, 1 H, CH=C-Cl), and 7.2 ppm (m, 4 H, **arom**).

3-Phenylindan-1-one. This was prepared in 40% yield by the procedure of Baker[22] and coworkers involving the reaction of

Table II
Chemical Shifts and Assignments of the Nmr Absorptions Integrated during the Rearrangement Studies

Substituent	Inden-1-yl derivative	Product	Internal standard
$-OH$	5.1 (bs, CHOH)	2.0 (m, $CH_2C{=}O$) and 2.4 (m, CH_2-arom)[a]	D[b]
$-CH_3$	0.8 (d, CH_3)	1.4 (m, CH_3)	H[c]
$-H$	2.5 (d, CH_2)	2.5 (d, CH_2)[d]	H
$-OCH_3$	2.7 (s, OCH_3)	3.2 (s, CH_3)	H
$-CH_2OH$	3.4 (m, $CHCH_2OH$)	3.2 (m, CH_2-arom) and 4.4 (m, CH_2OH)	D
$-OAc$	1.5 (s, $O\text{-}C(O)CH_3$)	1.7 (s, $O\text{-}C(O)CH_3$)	D
$-OPNB$	[e]	2.8 (d, CH_2)	H
$-ODNB$	[e]	2.8 (d, CH_2)	H
$-Cl$	4.7 (bs, CHCl)	2.6 (d, CH_2)	H
$-Ph$	4.6 (CHC_6H_5)	2.2 (d, CH_2)	H
$-CO_2H$	[f]	2.8 (bs, CH_2)	H

[a] Final product is indan-1-one. [b] Cyclododecane 0.7 (s, CH_2). [c] Cyclohexane 0.8 (s, CH_2). [d] The rearrangement product is 1-deuterioindene. [e] It was not possible to successfully integrate any protons of the starting material due to their close proximity to the pyridine solvent. [f] Unable to observe the α proton of indene-1-carboxylic acid because of the rapid rearrangement in pyridine.

trans-cinnamic acid with benzene in the presence of aluminum chloride followed by recrystallization from 2:1 petroleum ether–ether: mp 77–78° [lit.[22] mp 78°]; nmr (CCl_4) 2.6 (q, J = 4 and 19 Hz, 1 H, CH_2), 3.0 (q, J = 8 and 19 Hz, 1 H, CH_2), 4.5 (q, J = 4 and 8 Hz, 1 H, $CH\text{-}CH_2$), and 7.2 ppm (m, 9 H, **arom**).

3-Phenylindan-1-ol. A crude sample of this material was prepared in 88% yield by the reduction of 3-phenylindan-1-one with lithium aluminum hydride in ether: mp 75–88° (lit.[23] 95°); nmr (CCl_4) δ 1.8 (m, 1 H, CH_2) 2.8 (m, 1 H, CH_2), 3.0 (m, 1 H, OH), 3.9 (t, J = 8 Hz, 1 H, $CH\text{-}C_6H_5$), 5.0 (t, J = 8 Hz, 1 H, CHOH), and 7.0 ppm (m, 9 H, **arom**).

1-Phenylindene. This was prepared in 82% yield following the method of Marechal and Hamy[24] *via* heating 3-phenylindan-1-ol with anhydrous magnesium sulfate at 160° (0.9 mm): bp 111–114° (0.9 mm); nmr (CCl_4) δ 4.1 (m, 1 H, $CH\text{-}C_6H_5$), 6.1 (doublet of doublets, J = 2 and 6 Hz, 1 H, $=CH\text{-}CH\text{-}C_6H_5$), 6.4 (doublet of doublets, J = 2 and 6 Hz, 1 H, CH-arom), and 6.7 ppm (m, 9 H, **arom**).

3-Phenylindene. A mixture of 1-phenylindene and 3-phenylindene (0.6 g, 0.0031 mol) was mixed with 0.2 ml of triethylamine and distilled to yield 0.35 g (58%) of 3-phenylindene: bp 117–119° (0.3 mm) [lit.[25] bp 113–116° (0.4 mm)]; nmr (CCl_4) δ 3.4 (d, J = 2 Hz, 2 H, CH_2), 6.7 (t, J = 2 Hz, 1 H, $=CH\text{-}CH_2$), and 7.7 ppm (m, 9 H, **arom**).

Indene-1- and -3-carboxylic Acids. A solution of phenyllithium in 170 ml of ether was prepared by the reaction of 0.99 g (0.142 mol) of metallic lithium and 11.2 g (0.071 mol) of bromobenzene. Then 8.5 g (0.073 mol) of indene in 25 ml of ether was added dropwise, and the solution was stirred for 15 min at room temperature, cooled to −78°, and poured rapidly into 300 g of freshly crushed solid carbon dioxide. The resulting slurry was stirred briefly and then poured into 300 ml of rapidly stirred 10% aqueous hydrochloric acid at 0°. Work-up and recrystallization from 30–60° petroleum ether afforded 2.2 g (23%) of a mixture consisting mainly of the indene-1-carboxylic acid as cream colored crystals: mp 73–77° (lit.[8] mp 73–74°); nmr ($CDCl_3$) δ 4.6 (bs, 1 H, $CH\text{-}CO_2H$), 6.8 (doublet of doublets, J = 6 and 2 Hz, 1 H, =CH-arom), 7.1 (doublet of doublets, J = 6 and 2 Hz, 1 H, CH=CH-arom), 7.6 (m, 4 H, **arom**), and 11.9 ppm (s, 1 H, CO_2H). There was also obtained 5.3 g (55%) of indene-3-carboxylic acid as orange needles: mp 158–161° (lit.[26] mp 158–159°); nmr ($CDCl_3$) δ 3.5 (d, J = 2 Hz, 2 H, CH_2), 7.4 (m, 3 H, **arom**), 7.6 (t, J = 2 Hz, 1 H, $=CH\text{-}CH_2$), 8.1 (m, 1 H, **arom**), and 11.4 ppm (bs, 1 H, CO_2H).

Procedure for Rearrangement Studies. In the usual procedure where the rates of rearrangement were not too rapid (acetoxy or slower) or the substituted indene did not present solubility problems, *ca.* 0.2 g of the substituted indene, *ca.* 0.3 g of pyridine (redistilled from CaH_2), and *ca.* 20 mg of cyclododecane internal standard were carefully weighed using an analytical balance into an nmr tube. The tube was swept with nitrogen and sealed, and the contents were mixed well. The tube was then placed into a constant temperature oil bath at 40.7 ± 0.2° and the appropriate regions of the nmr spectrum were integrated at six or seven convenient intervals during the course of the rearrangement. An infinity point was measured after approximately 10 half-lives for rearrangement. The chemical shifts in pyridine and assignments of the absorptions in the nmr spectra which were integrated for each of the internal standards, inden-1-yl and inden-3-yl derivatives, for the purposes of following the rearrangements are given in Table II. These chemical shifts are only approximate since they varied slightly with concentration from run to run. In cases where the rearrangements were slow, several integrations of each region were taken for high accuracy. However, in cases where the rearrangements were fast only one integration of each region was taken. Where the rates of rearrangement were very fast, the tube was left in the probe during the entire run. For the purposes of rate constant calculations, the times during which the tube was in the probe (temperature 39.5 ± 1.5°) in all cases were included in the rearrangement times. In representative cases after a run was completed, the volume of the reaction mixture, needed for calculation of second-order rate constants, was measured by determining the weight of an equal volume of water. From these volume measurements, it was found that the densities of all of the various solutions were 1 g/ml within about 5% deviation. Thus, for all of the concentration calculations reported in Table I the volume in milliliters of the reaction mixture was taken as equivalent to its weight in grams.

Acknowledgment. We wish to thank the Committee on Research of the University of California, Davis for partial support of this study.

Registry No.—Indan-1-one, 83-33-0; 1-deuterioindan-1-ol, 53820-82-9; 3-deuterioindene, 933-61-9; inden-1-ol, 53820-83-0; 3-methylindan-1-one, 6072-57-7; 3-methylindan-1-ol, 22339-44-2; 1-methylindene, 767-60-2, 3-methylindene, 767-59-9; 1-methoxyindene, 27973-23-5; trimethyl orthoformate, 149-73-5; 3-methoxyindene, 53820-84-1; 1-hydroxymethylindene, 2471-87-6; 3-hydroxymethylindene, 2471-88-7; 1-acetoxyindene, 19455-83-5; 3-acetoxyindene, 35116-20-2; inden-1-yl *p*-nitrobenzoate, 53820-85-2; *p*-nitrobenzoyl chloride, 122-04-3; inden-3-yl *p*-nitrobenzoate, 53820-86-3; inden-1-yl 3,5-dinitrobenzoate, 53820-87-4; 3,5-dinitrobenzoyl chloride, 99-33-2; inden-3-yl 3,5-dinitrobenzoate, 53820-88-5; 1-chloroindene, 25894-22-8; 3-chloroindene, 53820-89-6; 3-phenylindan-1-one, 16618-72-7; 3-phenylindan-1-ol, 30516-40-6; 1-phenylindene, 1961-97-3; 3-phenylindene, 1961-96-2; indene-1-carboxylic acid, 14209-41-7; indene-3-carboxylic acid, 5020213.

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Synthesis of Some 1-Imidoyl-2-(3-indolyl)-1,2-dihydroquinolines and -isoquinolines *via* Reissert-Type Condensations

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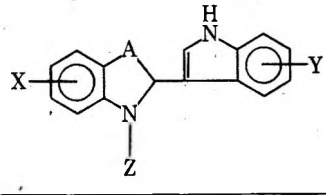
Received June 4, 1974

The reaction of *N*-imidoylcycloimmonium salts with indoles was used for the preparation of some 1-imidoyl-2-(3-indolyl)-1,2-dihydroquinolines (1) and -isoquinolines (2). Catalytic hydrogenation of these compounds gave the 1,2,3,4-tetrahydro derivatives. Various members of these series of compounds were alkylated at the indole nitrogen. The scope and some limitations of the reaction are presented.

We have been interested in 1-imidoyl-2-(3-indolyl)- and (2-indolyl)indolines for their biological effects[1] as well as a novel rearrangement[2] exhibited by some members of the series. In seeking to structurally extend this class of compounds, we developed a versatile reaction for the preparation of 1-imidoyl-2-(3-indolyl)-1,2-dihydroquinolines (1) and 2-imidoyl-1-(3-indolyl)-1,2-dihydroisoquinolines (2); their tetrahydro derivatives, 4 and 7; and their indolic N-alkylated derivatives, 3, 5, 6, and 8 (Scheme I).

von Dobeneck and Goltzsche,[3] and later Bergman,[4] applied nucleophilic attack of indole on *N*-acylcycloimmonium salts to form adducts 9[3,4] and 10.[3] We envisioned the possibility of extending the nucleophilic attack to N-imidoylated quinoline salts, either actual (12) or incipient (11),

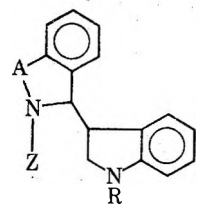
Table I
1-Imidoyl-2-(3-indolyl)quinolines



Compd	A	X	Y	Z	Yield,[a] %	Mp, °C	Formula	Analysis[b]
1a	CH=CH	H	H	-CH=NCHMe$_2$	15	187.5–189 dec	$C_{21}H_{21}N_3 \cdot HCl$	C, H, N
1b	CH=CH	H	5-OMe	-CH=N(c-C$_6$H$_{11}$)	7	174–177	$C_{25}H_{27}N_3O \cdot HCl$	C, H, N
1c	CH=CH	5,6-Benzo	H	5,5-Dimethyl-1-pyrrolin-2-yl	14	222–223	$C_{27}H_{25}N_3 \cdot HCl$	C, H, N, Cl
1d	CH=CH	6-OMe	5-OMe	5,5-Dimethyl-1-pyrrolin-2-yl	37	200–203 dec	$C_{25}H_{27}N_3O_2 \cdot HCl$	C, H, N, Cl
1e	CH=CH	3,4-Benzo	H	1-Pyrrolinyl-2-yl	5	119.5–128.5 dec	$C_{25}H_{21}N_3 \cdot \frac{1}{2}C_6H_{14}O$	C, H, N
1f	CH=CH	H	H	1-Pyrrolinyl-2-yl	9	219.5–220.5	$C_{21}H_{19}N_3$	C, H, N
3a	CH=CH	H	N-Me	5-Methyl-1-pyrrolinyl-2-yl	10	175–177	$C_{23}H_{23}N_3$	C, H, N
4a	CH_2CH_2	6-OMe	5-OMe	5,5-Dimethyl-1-pyrrolin-2-yl	65	226.5–229.5	$C_{25}H_{29}N_3O_2 \cdot HCl$	C, H, N, Cl
4b	CH_2CH_2	H	H	1-Pyrrolinyl-2-yl	67	228–229	$C_{21}H_{21}N_3 \cdot HCl$	C, H, N, Cl
5a	CH_2CH_2	H	N-Me	-CH=NCHMe$_2$	52	108–111.5	$C_{22}H_{25}N_3$	C, H, N

[a] For the tetrahydro and *N*-alkyl analogs, the yield refers to conversion from the dihydro compounds. [b] The analytical data were acceptable if within 0.4% for C and 0.3% for other elements.

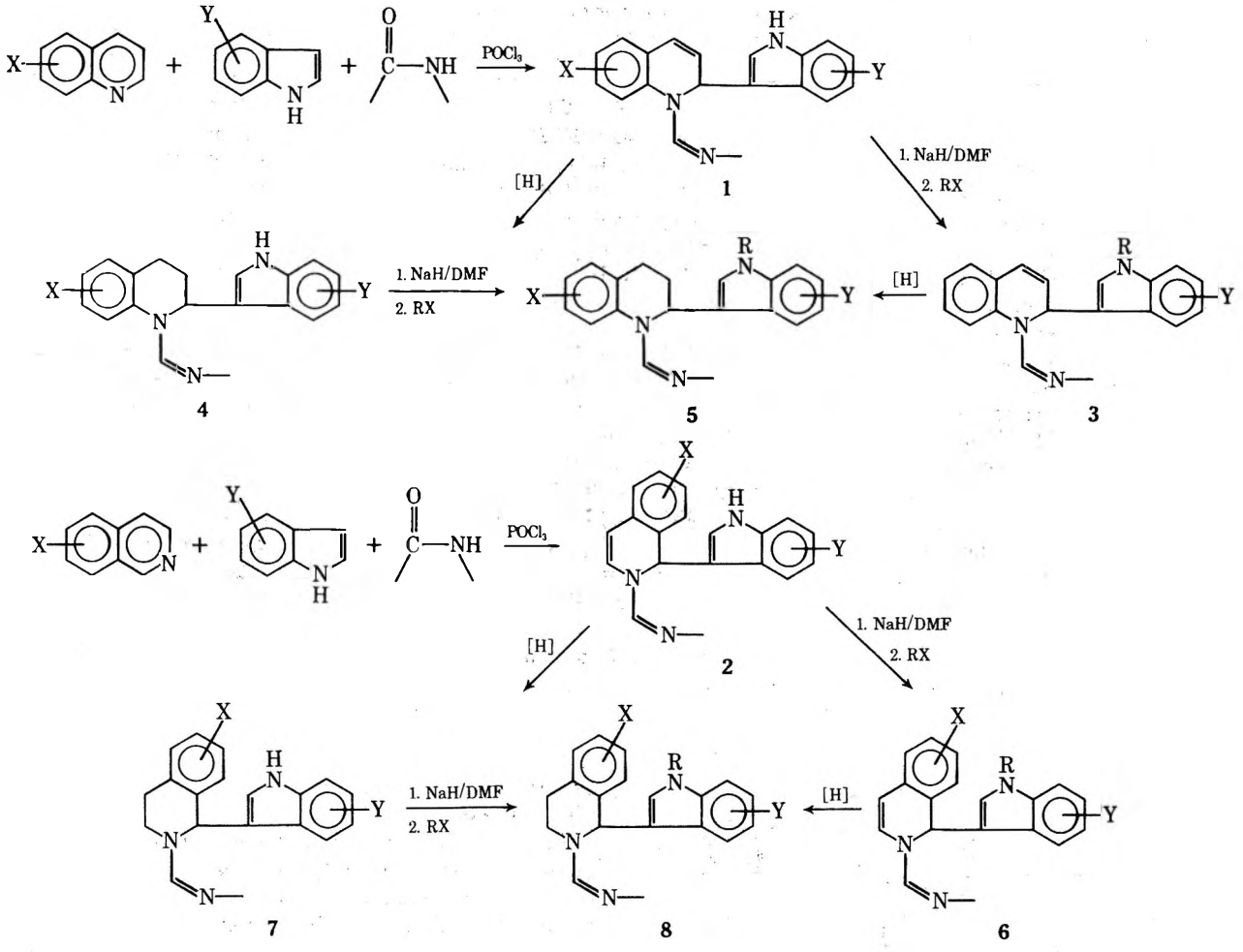
Table II
2-Imidoyl-1-(3-indolyl)isoquinolines

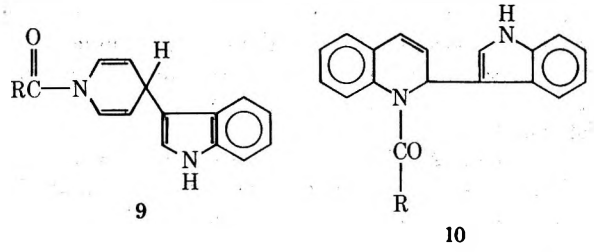


Compd	A	R	Z	Yield,[a] %	Mp, °C	Formula	Analysis[b]
2a	CH=CH	H	-CH=NCHMe$_2$	17	144–145.5	$C_{21}H_{21}N_3$	C, H, N
2b	CH=CH	H	5,5-Dimethylpyrrolin-2-yl	65	191.5–192	$C_{23}H_{23}N_3$	C, H, N
2c	CH=CH	H	1-Pyrrolin-2-yl	13	160–162.5	$C_{21}H_{19}N_3$	C, H, N
6a	CH=CH	Me	1-Pyrrolin-2-yl	65	186–189	$C_{22}H_{21}N_3$	C, H, N
7a	CH_2CH_2	H	5,5-Dimethylpyrrolin-2-yl	60	281–283.5 dec	$C_{23}H_{25}N_3 \cdot HCl$	C, H, N, Cl
8a	CH_2CH_2	Me	1-Pyrrolin-2-yl	69	167–168.5	$C_{22}H_{23}N_3$	C, H, N

[a] For the tetrahydro and *N*-alkyl analogs, the yield refers to conversion from the dihydro compounds. [b] The analytical data were acceptable if within 0.4% for C and 0.3% for other elements.

Scheme I





on the basis of the mechanistic sequence given in Scheme II.

Results

Table I lists some 1-imidolyl-2-(3-indolyl)quinolines prepared by this reaction. Table II lists some 2-imidoyl-1-(3-indolyl)isoquinolines. By varying the components we investigated the scope and limitations of the reaction. Table III summarizes variations of the reactions which did not produce desired products.

Spectra of the reaction products agreed with assignment of structures **1** and **2** analogous to spectral correlations for the imidoyl indolylindolines.[2] Although uv and ir spectra were consistent, NMR and mass spectra were more definitive.

NMR spectra of pyrrolinyl dihydroquinolines **16** and isoquinolines **17** exhibited the H-8 proton peaks at a chemical shift more downfield (~7.8–8.2 Hz, depending on substituents and solvent) than the other aromatic protons. This is attributable to the effect of magnetic anisotropy of the imino group upon H-8 in **16**[2] and the indolyl π system on H-8 in **17**. Mass spectra of these compounds gave a *m/e* 245

Scheme II

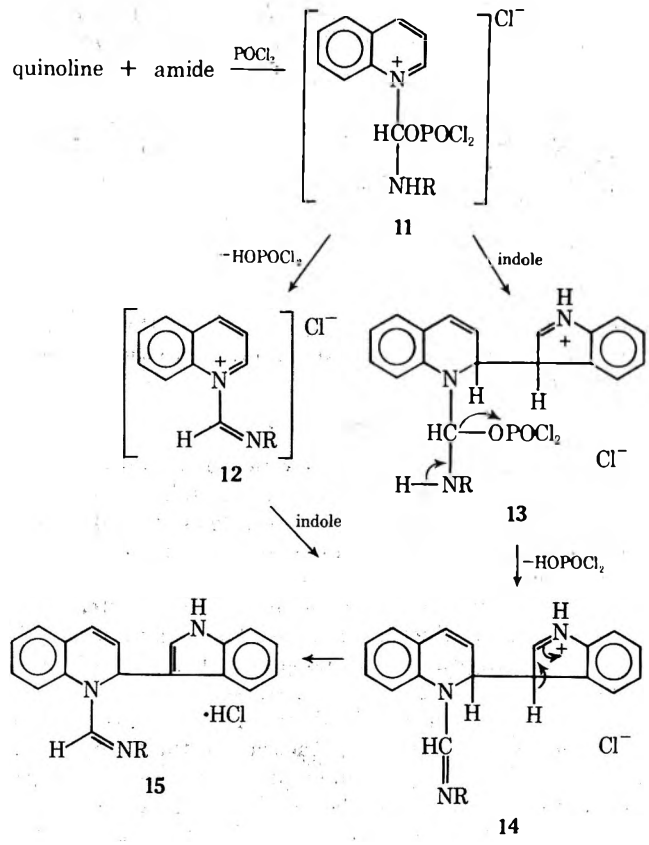
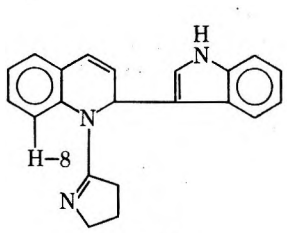


Table III
Reaction Component Variations[a]

Reaction	Base	Carboxamide	Nucleophile
1	Pyridine	$HC(=O)NHC(CH_3)_3$	Indole
2	Pyridine	$HC(=O)NHCH(CH_3)_2$	Skatole
3	Quinoline	5-Methyl-2-pyrrolidinone	2-Methylindole
4	Quinoline	$HC(=O)NHCH_2CH_3$	Skatole
5	Quinoline	Caprolactam	Indole
6	Quinoline	$HC(=O)NHCH_2N(CH_3)_2$	Indole
7	Quinoline	2-Pyrrolidinone	Pyrrole
8	Quinoline	2-Pyrrolidinone	KCN
9	Quinoline	$HC(=O)NHCH(CH_3)_2$	7-Azaindole
10	Quinoline	5-Methyl-2-pyrrolidinone	Imidazole[1,2-*a*]pyridine
11	Quinoline	$HC(=O)NHCH(CH_3)_2$	Dimethylaniline
12	Quinoline	$HC(=O)NHCH(CH_3)_2$	Diethyl malonate
13	Quinoline	Valerolactam	Indole
14	Isoquinoline	Valerolactam	Skatole
15	Isoquinoline	$HC(=O)NHCH_2CH_3$	Skatole
16	4-Phenylpyrimidine	$HC(=O)NHCH_2CH_3$	Indole
17	7-Azaindole	$HC(=O)NHCH(CH_3)_2$	7-Azaindole
18	1-Methylimidazole	$C_6H_5C(=O)Cl$	Indole
19	Quinaldine	2-Pyrrolidinone	Indole
20	Acridine	2-Pyrrolidinone	Indole
21	Lepidine	2-Pyrrolidinone	Indole

[a] These variations did not result in formation of an amidine product.



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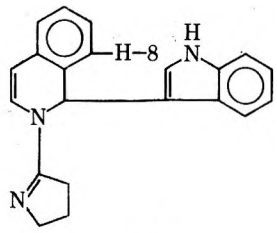
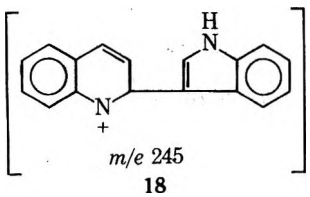
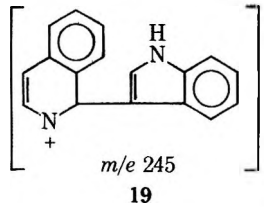


17

fragment in high abundances. This would correspond to fragment structure **18** or **19**. This assignment has been cor-



18



19

roborated by the predictable *m/e* change of the abundant fragment when substituents were attached to the heterocyclic ring systems.

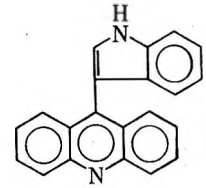
Discussion

The two main considerations which determined experimental success of the reaction were the stability of the intermediate and the activity of the nucleophile under reaction conditions. The N-imidoylated cycloimmonium salt intermediate, e.g., **11** (or **12**), seemed less stable than a corresponding *N*-acyl cycloimmonium salt. The shorter intermediate lifetime which resulted was demonstrated as follows: if the introduction of indole was delayed until after equilibration of the quinoline, carboxamide, and $POCl_3$, no amidine product was obtained. In other words, one factor responsible for success of the reaction was the ability of the base to stabilize the cycloimmonium salt intermediate. The added stabilization of the benzo ring, when quinoline or isoquinoline functioned as the base, also was critical to the success of the reaction since the reaction failed with pyridine as the base.

The second major factor to be taken into account was the potency of the nucleophile under reaction conditions. The extent of basic character that a nucleophile possessed inversely affected nucleophilic strength in this acidic reaction milieu owing to ready protonation. The negative results outlined in Table III would indicate that the requisite nucleophilicity fell within a rather narrow range.

In addition to the electronic considerations, steric hindrance is important in determining nucleophilic potency. Owing to the apparent close steric tolerances for reaction success,[5] we feel that **13** is more likely the reaction intermediate (see Scheme II).

The product **20** which resulted from reaction 20 in Table III demonstrates the similarity between the *N*-imidoylacridinium ion and the *N*-acylacridinium ion, because **20** has

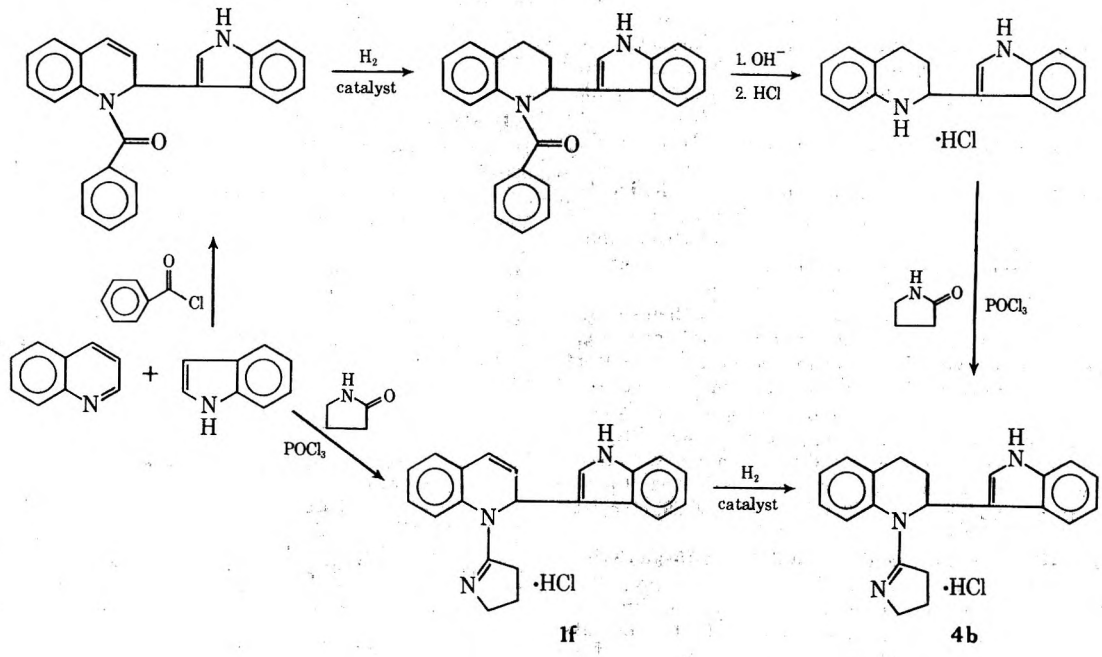


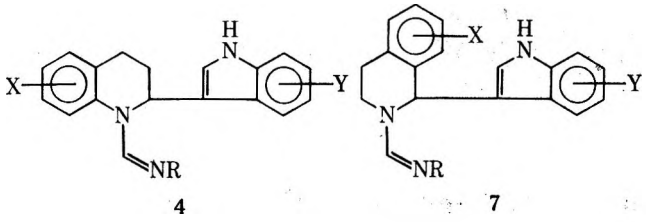
20

been reported[6] previously as arising from indole attack on the *N*-acylacridinium ion followed by oxidative elimination. The importance of the *N*-imidoylacridinium ion was confirmed by the fact that no reaction took place when acridine was treated with indole and $POCl_3$ without a carboxamide.

Reduction and Alkylation Products. Some synthetic modifications of the dihydro compounds were made. The 1-imidoyl-2-(3-indolyl)-1,2,3,4-tetrahydroquinolines **4** and 2-imidoyl-1-(3-indolyl)-1,2,3,4-tetrahydroisoquinolines **7** were conveniently prepared by catalytic hydrogenation of the corresponding dihydro analogs. Spectra of the tetrahydro compounds were consistent with assignment of structure. Again the salient spectral features were a downfield

Scheme III





4 7

shift of the H-8 proton in NMR spectra of pyrrolinyl derivatives and the high abundance of fragment *m/e* 247 in mass spectra. This fragment corresponded to the tetrahydro analog of **18** or **19**, strengthening that structural assignment. A correlation scheme confirmed structural assignments for both series (Scheme III).

The most direct synthesis of *N*-alkylindole derivatives of imidoylquinolines and isoquinolines would involve the use of an *N*-alkylindole as the starting material. Unfortunately, this process was not general with *N*-alkylindoles and the desired product formed only in isolated instances. We found, as an alternative, that the indolic nitrogen could be selectively alkylated under mild conditions starting with an imidoylquinoline or isoquinoline from either the di- or tetrahydro series. The critical feature in this process was the irreversible formation of the anion under mild conditions, a prerequisite which the NaH–DMF system fulfilled quite well. Other base systems were not satisfactory. Potassium *tert*-butoxide in *tert*-butyl alcohol, for example, led to a mixture of alkylated and nonalkylated products owing to the reversibility of the butoxide–indole anion system.

Structure assignment of the *N*-alkylindole derivatives was straightforward. In the NMR spectra, the characteristic indolic N–H proton (> δ 8.5 Hz) disappeared and was replaced by an *N*-alkyl pattern displayed at about 3.5–4.0 Hz. The fragmentation pattern of the mass spectrum did not change from the N–H series. The major fragmentation was the loss of the imidoyl group which gave rise to a characteristic base peak for each series.

Experimental Section

NMR spectra were recorded on either a Varian A-60 or XL-100 spectrometer with tetramethylsilane as an internal standard. Ir spectra were taken on either a Beckman Model IR 8 or IR 18A. Mass spectral data were obtained from a CEC 21-104 mass spectrometer. Melting points were determined with a Thomas-Hoover capillary apparatus and are corrected. Satisfactory analytical and spectra data were obtained on all of the compounds. A single experimental procedure is provided for a representative compound from each class.

The Dihydroquinoline and Dihydroisoquinoline Series. 3,4-Dihydro-4-(5,5-dimethyl-1-pyrrolin-2-yl)-3-indol-3-yl-benzo[*f*]quinoline Hydrochloride (1c). A solution of $POCl_3$ (4.60 g, 0.03 mol) in 10 ml of benzene was added dropwise to a stirred solution of 5,6-benzoquinoline (10.62 g, 0.06 mol), indole (3.51 g, 0.03 mol), 5,5-dimethyl-2-pyrrolidinone (3.39 g, 0.03 mol), and benzene (20 ml) over a period of 15 min. The reaction mixture was mildly exothermic and a tar precipitated. The reaction mixture was stirred for approximately 24 hr, at which time the benzene supernatant was decanted and discarded. The reaction tar was washed with H_2O and then stirred in Me_2CO. The tar went into solution, and a light yellow solid precipitated which was isolated by filtration. The solid was slurried in distilled H_2O and made basic with concentrated NH_4OH. This basic mixture was extracted with chloroform. The chloroform extracts were combined and concentrated to an off-white solid which was washed with hot hexane and recrystallized from isopropyl ether (mp 130–133.5°). Absolute ethanol was added to the solid, and the mixture was stirred until most of the solid was in solution. This mixture was filtered, and the stirred filtrate was treated with an excess of ethanolic HCl. The solution was triturated and chilled. Several crops of white solid were isolated to give 1.8 g of **1c** (14% yield), mp 222–223°. Anal. Calcd for $C_{27}H_{25}N_3 \cdot HCl$: C, 75.77; H, 6.12; N, 9.82; Cl, 8.29. Found: C, 75.59; H, 6.14; N, 9.63; Cl, 8.10.

1,2-Dihydro-1-(3-indolyl)-2-(5,5-dimethyl-1-pyrrolin-2-yl)isoquinoline (2b). The compound was prepared with a procedure similar to the one used for **1c** with the exception that the base was isolated. Recrystallization from benzene gave 3.5 g of white solid (65% yield), mp 191.5–192°. Anal. Calcd for $C_{23}H_{23}N_3$: C, 80.90; H, 6.79; N, 12.31. Found: C, 80.96; H, 6.68; N, 12.38.

Tetrahydroquinoline and Tetrahydroisoquinoline Series. 1-(5,5-Dimethyl-1-pyrrolin-2-yl)-1,2,3,4-tetrahydro-6-methoxy-2-(5-methoxy-3-indolyl)quinoline Hydrochloride (4a). 1-(5,5-Dimethyl-1-pyrrolin-2-yl)-1,2-dihydro-6-methoxy-2-(5-methoxy-3-indolyl)quinoline hydrochloride (**1d**, 1.54 g, 0.0035 mol, prepared in the same manner as **1c**) was dissolved in 200 ml of absolute ethanol and 1 ml of ethanolic HCl with slight warming. This solution was poured into a Parr bottle containing 0.2 g of PtO_2 and hydrogenated on a Parr apparatus beginning at 50 psi. The theoretical amount of hydrogen was absorbed in 3 min; and after 15 min, no additional hydrogen uptake was observed. After the catalyst was removed by filtration, the solution was evaporated in vacuo to a pink foam. This foam was recrystallized in approximately 100 ml of acetone to give 1.0 g (65% yield) of a light pink solid, mp 226.5–229.5°. Anal. Calcd for $C_{25}H_{29}N_3O_2 \cdot HCl$: C,

68.24; H, 6.87; N, 9.85; Cl, 8.06. Found: 68.28; H, 6.77; N, 9.42; Cl, 8.02.

1,2,3,4-Tetrahydro-1-(3-indolyl)-2-(5,5-dimethyl-1-pyrrolin-2-yl)isoquinoline Hydrochloride (7a). The compound was prepared from **2b** with a procedure similar to the one used for **4a**. Recrystallization from isopropyl alcohol gave a 60% yield of a pink solid, mp 281.5–283.5°. Anal. Calcd for $C_{23}H_{25}N_3 \cdot HCl$: C, 72.71; H, 6.90; N, 11.06; Cl, 9.33. Found: C, 72.60; H, 6.80; N, 10.84; Cl, 9.48.

The 1-Alkylindole Derivatives. Method A. 1,2-Dihydro-1-(1-methyl-3-indolyl)-2-(1-pyrrolin-2-yl)isoquinoline (6a). A solution of 1,2-dihydro-1-(3-indolyl)-2-(1-pyrrolin-2-yl)isoquinoline (**2c**, 4.6 g, 0.015 mol) in 110 ml of DMF (dried over molecular sieves) was first treated under a nitrogen atmosphere, with sodium hydride (57% mineral oil dispersion, 0.70 g, 0.015 mol), then stirred for 3 hr, and finally treated with a solution of iodomethane (2.1 g, 0.015 mol) in 15 ml of DMF (dried over molecular sieves). After being stirred for an additional 24 hr, the reaction mixture was filtered. The clear yellow filtrate was poured into approximately 300 ml of stirred ice water, and the resulting precipitate was filtered, dried (vacuum oven at 65°), and recrystallized from EtOAc to give 3.2 g (65% yield) of an off-white solid, mp 186–189°. Anal. Calcd for $C_{22}H_{21}N_3$: C, 80.70; H, 6.47; N, 12.83. Found: C, 80.89; H, 6.21; N, 12.71.

Method B. 1,2-Dihydro-2-(1-methyl-3-indolyl)-1-(5-methyl-1-pyrrolin-2-yl)quinoline (3a). The compound was prepared from 1-methylindole, 5-methyl-2-pyrrolidinone, and quinoline according to the procedure given for the synthesis of **1c**. Compound **3a**, purified as the free base, had mp 175–177°. Anal. Calcd for $C_{23}H_{23}N_3$: C, 80.90; H, 6.79; N, 12.31. Found: C, 80.75; H, 6.64; N, 12.48.

Acknowledgment. The authors wish to thank P. S. Schrecker and C. I. Kennedy for their contributions to structural analysis and R. E. Yeager for technical assistance. A special thanks is given to C. Combs by the authors for his invaluable aid and helpful suggestions in structural determination.

Registry No.—**1a**, 53159-51-6; **1b**, 53019-08-2; **1c**, 53019-07-1; **1d**, 53018-88-5; **1e**, 53019-04-8; **1f**, 53089-20-6; **2a**, 53018-80-7; **2b**, 53018-83-0; **2c**, 53018-81-8; **3a**, 53019-00-4; **4a**, 53159-52-7; **4b**, 53018-85-2; **5a**, 53881-35-9; **6a**, 53018-99-8; **7a**, 53089-14-8; **8a**, 53019-02-6; quinoline, 91-22-5; isoquinoline, 119-65-3; 5,6-benzoquinoline, 85-02-9; 6-methoxyquinoline, 5263-87-6; 3,4-benzoquinoline, 229-87-8; indole, 120-72-9; 5-methoxyindole, 1006-94-6; *N*-methylindole, 603-76-9; *N*-isopropylformamide, 16741-46-1; *N*-cyclohexylformamide, 766-93-8; 5,5-dimethyl-2-pyrrolidinone, 5165-28-6; 2-pyrrolidinone, 616-45-5; 5-methyl-2-pyrrolidinone, 108-27-0.

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(3) H. von Dobeneck and W. Goltzsche, *Chem. Ber.*, **95**, 1484 (1962).
(4) J. Bergman, *J. Heterocycl. Chem.*, **7**, 1071 (1970).
(5) This is a feature noted previously for imidoylation of the indolylindolines.[2] Increased ring size or a substituent in the 7 position of the indoline ring prevented imidoylation of the 2-(3-indolyl)indolines.
(6) A. K. Sheinkman, S. G. Potashnikova, and S. N. Baranov, *Khim. Geterotsikl. Soedin*, 1292 (1970); *Chem. Abstr.*, **74**, 125377n (1971); A. K. Sheinkman, A. N. Kost, S. G. Potashnikova, A. O. Ginzburg, and S. N. Baranov, *Khim. Geterotsikl. Soedin*, 648 (1971); *Chem. Abstr.*, **76**, 72342e (1972).
(7) Prepared by the procedures in "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N.Y., 1963, pp 357, 652.

Rearrangement of 1,2-Dihydro-2-(3-indolyl)-1-[2-(1-pyrrolinyl)]quinolines to 9-(3-Indolylvinyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolines[1]

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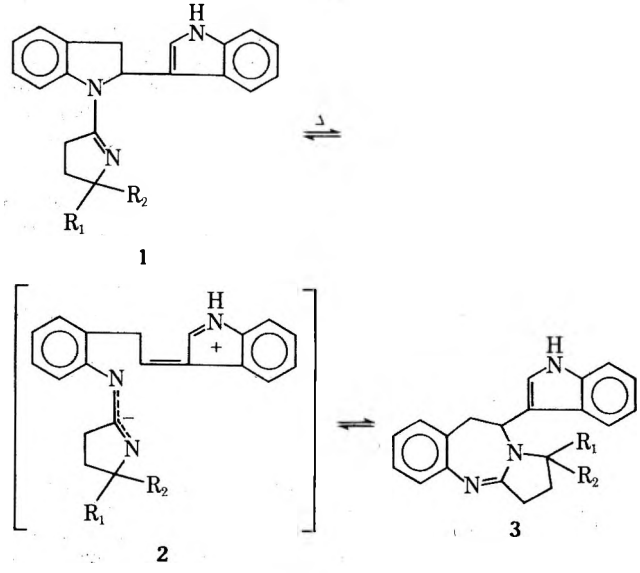
Received June 4, 1974

A series of 1,2-dihydro-2-(3-indolyl)-1-[2-(1-pyrrolinyl)]quinolines (**4**) undergoes a novel rearrangement to 9-(3-indolylvinyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolines (**10**). The structures of the rearranged products were assigned spectroscopically and further confirmed by a structure correlation scheme. A mechanism for the rearrangement is proposed and discussed in terms of kinetic and structural data.

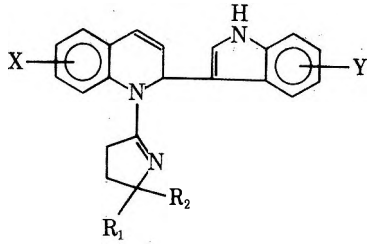
In the course of work with 1-imidoyl-2-(2- and 3-indolyl)indolines,[2a] we reported[2b] the interconversion of 2-(3-indolyl)-1-[2-(1-pyrrolinyl)]indoles, **1**, to 2,3,5,6-tetrahydro-5-(3-indolyl)-1*H*-pyrrolo-[2,1-*b*][1,3]benzodiazepines **3**. The postulated mechanism for this interconversion (Scheme I) involves a reversible ring opening to give the intermediate **2**, which undergoes ring closure after geometric isomerization. Because of the novelty of this rearrangement and a desire to determine its scope, we extended our study to the reactions of 1,2-dihydro-2-(3-indolyl)-1-[2-(1-pyrrolinyl)]quinolines **4** and -isoquinolines **5** and the corresponding tetrahydro derivatives **6** and **7**, the preparations of which are described in the Experimental Section.

Scheme I



Results

Present in all of the compounds investigated was the structural fragment **8**; yet we found that only the 1,2-dihydro-2-(3-indolyl)-1-[2-(1-pyrrolinyl)]quinolines **4** underwent rearrangement. Moreover, the structures of the rearranged products were not the expected benzodiazocines **9** from analogy to the indolylindoline rearrangement, but were the stable pyrroloquinazolines, **10**.



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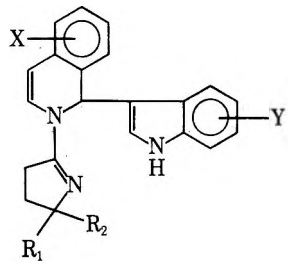
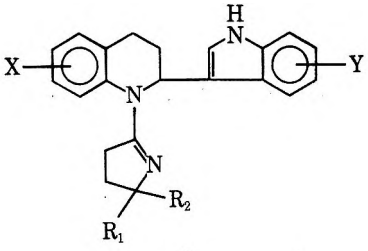


5

a, $R_1 = R_2 = H$; X = Y = H
b, $R_1 = H$; $R_2 = CH_3$; X = Y = H
c, $R_1 = R_2 = CH_3$; X = Y = H
d, $R_1 = R_2 = CH_3$; X = 7-OCH_3; Y = H
e, $R_1 = R_2 = CH_3$; X = 5,6-benzo; Y = H
f, $R_1 = H$; $R_2 = CH_3$; X = 7-OMe; Y = 5-OMe
g, $R_1 = R_2 = CH_3$; X = 7-OMe; Y = 5-OMe



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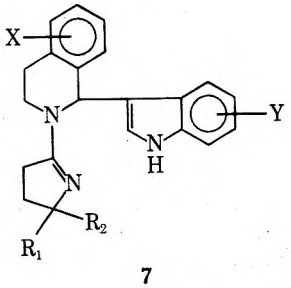

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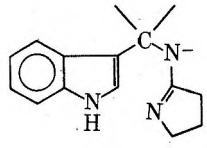
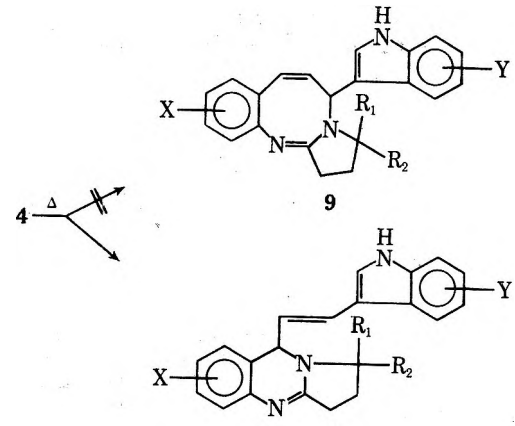


8

The NMR and mass spectral data were consistent with this structure assignment. The olefinic protons of the starting dihydroquinoline isomer **4** exhibited a typical cis coupling of 9.5 Hz. The olefinic protons in the rearranged product, however, exhibited a coupling constant of 15.8 Hz, more indicative of a trans double bond than the cis double bond expected in benzodiazocine **9**. The most salient piece of evidence from the mass spectrum of rearranged products was that the 100% peak for each analog corresponded to the ion left after the loss of the indolylvinyl moiety. This would correspond to a predicted fragmentation of the pyrroloquinazoline structure **10** but



9 10

a, $R_1 = R_2 = H$; X = Y = H
b, $R_1 = H$; $R_2 = CH_3$; X = Y = H
c, $R_1 = R_2 = CH_3$; X = Y = H
d, $R_1 = R_2 = CH_3$; X = 7-OCH_3; Y = H
e, $R_1 = R_2 = CH_3$; X = 7,8-benzo; Y = H
f, $R_1 = H$; $R_2 = CH_3$; X = 6-OMe; Y = 5-OMe
g, $R_1 = R_2 = CH_3$; X = 6-OMe; Y = 5-OMe

should not be so abundant in the fragmentation of the benzodiazocine **9**.

Various chemical studies were carried out with the pyrroloquinazoline structure. While treating **10** with ozone caused extensive fragmentation of the molecule, no simple cleavage products were isolated from the ozonized reaction mixture. The milder Lemieux–Johnson oxidation[4] and base hydrolysis also failed to give a meaningful structural fragment. The olefinic bond could be hydrated in acidic media under mild conditions or catalytically hydrogenated. These chemical studies failed to give any confirmatory data for structure assignment. A structure correlation scheme was therefore studied (Scheme II). In this scheme, hydrogenation converted the indolylvinyl group of **10a** to a less troublesome indolylethyl group in the correlation compound **11**. At the other end of the scheme, an indolylchalcone **12**, prepared by condensing o-nitroacetophenone with indole-3-carboxaldehyde, was hydrogenated to the hydroxyamino compound **13**, which was allowed to react with the 2-pyrrolidinone–$POCl_3$ adduct. Although the expected hydroxyamidine compound was not isolated, we were able to isolate and identify (TLC, ir, mass spectrum) a small amount of the correlation compound **11** from the tarry reaction mixture.[6] This scheme supported our pyrroloquinazoline structure assignment.

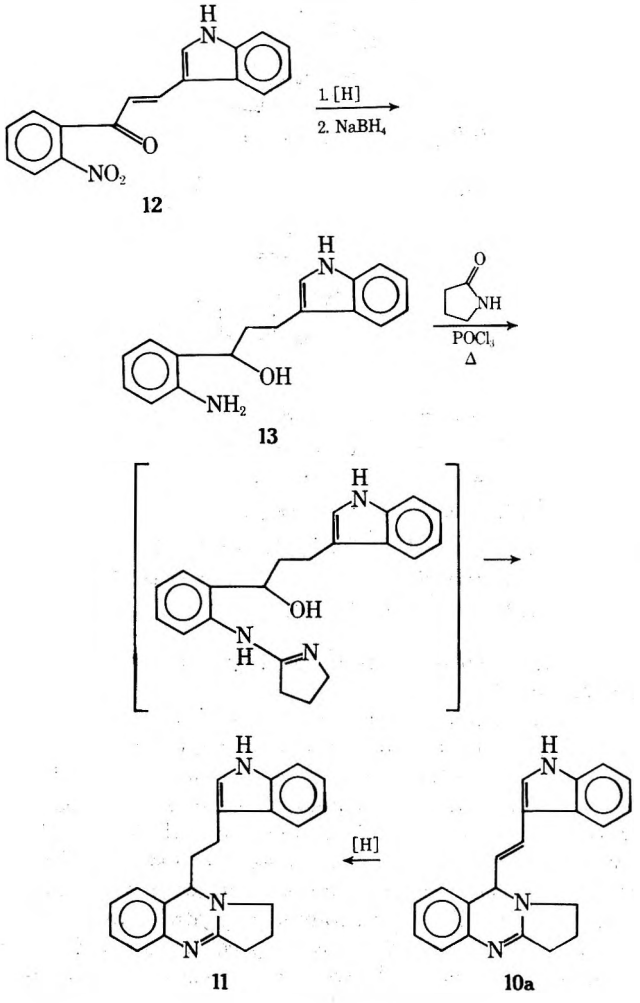
Mechanism

To begin our study of the rearrangement process, we examined the effect of substrate structure on the rearrangement. Only the dihydroquinoline class of analogs rearranged. Table I lists the structural variants which did not rearrange.

We studied the kinetics of the rearrangement with NMR using DMSO-d_6 as the solvent and 5-methylpyrrolinyl analogs as the substrates, e.g., **4b**, because they exist as pairs of diastereomers. Diastereoisomerism gives added capability for study of the reaction mechanism.

Experimentally, we found that the rearrangement is irreversible in contrast to the equilibrium process of the indolylindolines to benzodiazepines.[2b] Although the rearrangement appears to exhibit acidic as well as basic catalysis (Figure 1), the rate enhancement varies inversely with acid strength. Thus, 0.1 equiv of HCl enhanced rearrangement rate to a greater extent than did 1.0 equiv of HCl and the

Scheme II
Structure Correlation Scheme



use of trifluoroacetic acid retarded the reaction. Figure 1 shows that NH_4OAc increased the rate of rearrangement more than acetic acid.

The structural and kinetic data suggest the following

Scheme III
Rearrangement Mechanism

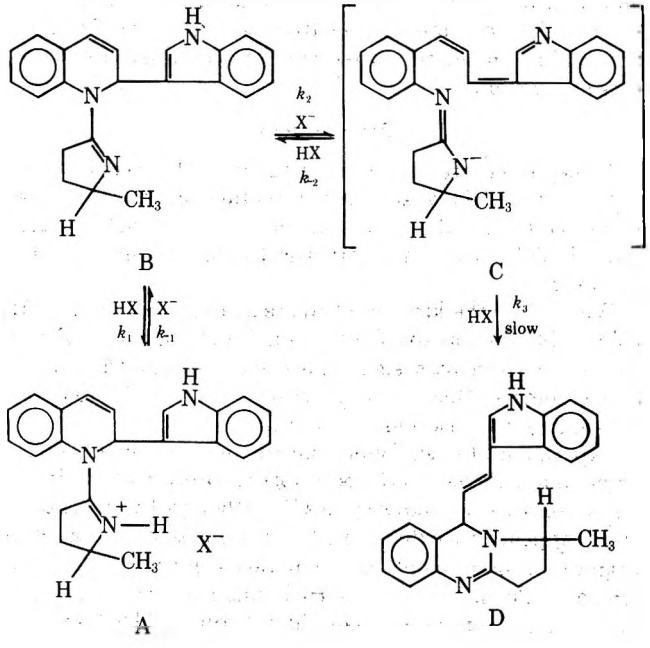
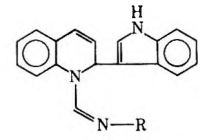
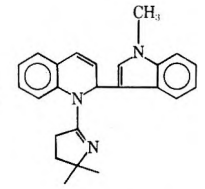
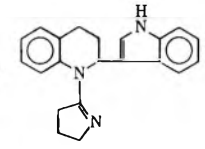
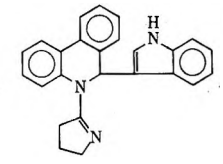
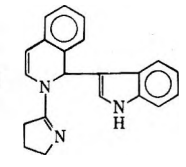
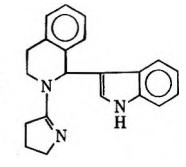


Table I
Imidoylquinolines and -isoquinolines Which Do Not Rearrange

No.	Structure	Variation
1		Linear imidoyl moiety
2		Indole N-methylation
3		1,2,3,4-Tetrahydroquinoline
4		3,4 bond incorporated into benzo ring
5		1,2-Dihydroisoquinoline
6		1,2,3,4-Tetrahydroisoquinoline

mechanism for the rearrangement (Scheme III). When the rearrangement occurs in acidic media, the dihydroquinoline isomer B can be protonated. The extent to which this occurs affects overall reaction rate by depleting the concentration of the dihydroquinoline base B, the species that undergoes ring opening to C. This is supported by the facts that (1) NH_4OAc enhances the rate more than HOAc, (2) 0.1 equiv of HCl enhances more than 1.0 equiv of HCl, and (3) 1.0 equiv of HOAc enhances more than 1.0 equiv of trifluoroacetic acid. In basic media, of course, this equilibrium can be ignored. The primary event leading to rearrangement is base abstraction of the indolic N–H to give the ring-opened intermediate C. This process, denoted by rate constant k_2, seems subject to general base catalysis. The reversibility of the ring-opening process is illustrated by the experiment using only one of the two diasteromeric pairs of **4b** (Table II). The starting dihydroquinoline diastereomer **4b-I** was completely equilibrated with the other in a time span in which only 8% of the rearranged pyrroloquinazoline was formed. The importance of proton abstraction is shown by complete inhibition of rearrangement when the indole nitrogen is methylated. This is in agreement with an earlier report[5] on related work in which indolenine formation is required for elimination of a group from the 3-indolyl α carbon.

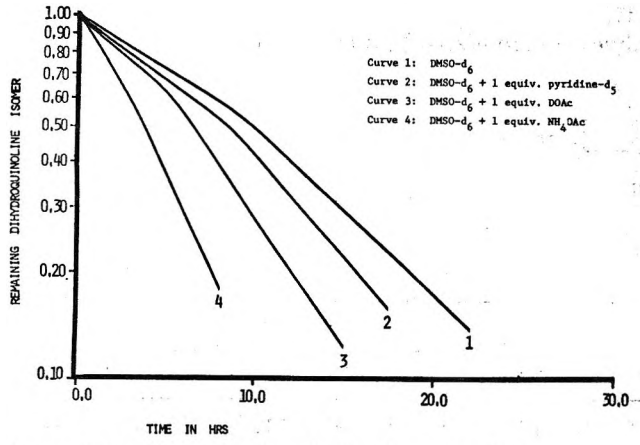
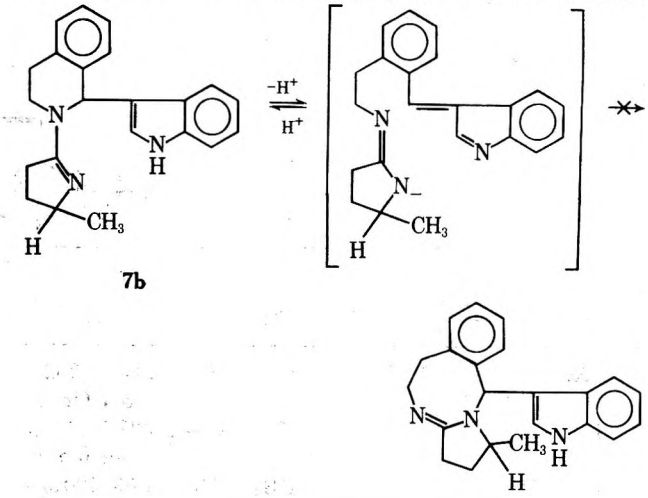


Figure 1. Remaining dihydroquinoline isomer vs. time.

Table II
Rearrangement of 4b Diastereomer I

Time, hr	4b-I, %	4b-II, %	Pyrroloquinazoline product 10b, %
0	100	0	0
1	80	20	0
7	52	40	8

Scheme IV
Isomerization of Tetrahydroisoquinoline Diastereomer



7b

Time, hr	7b-I, %	7b-II, %
0	30	70
2	40	60
4	44	56
7	48	52
15	54	46
30	54	46

Finally, ring closure to D occurs in the slow step, denoted by rate constant k_3. Only the dihydroquinolines are structurally capable of converting to the product indolylvinylpyrroloquinazolines. This class of analogs is still subject to some structural limitations. When the nucleophilicity of the attacking nitrogen in the slow step is lessened, e.g., by greater steric hindrance in linear imidoyl groups[7] (Table I, structure 1), the rearrangement does not proceed. It also fails if the attacked 3,4 double bond is part of an aromatic ring. Dihydroisoquinoline analogs do not possess the requisite structure necessary for this type of rearrangement. This applies also to the tetrahydroquinolines and tetrahydroisoquinolines. These structures could only rearrange to a benzodiazocine, the higher homolog of the indolylindoline rearrangement. No rearrangement has ever been detected in these cases, owing probably to the difficulty of formation and instability of the large ring product. According to our postulated mechanism, nothing should prevent ring opening for any particular amidine 4–7, since they each have incorporated into their structure fragment 8. This was tested. Heating a diastereomeric mixture enriched in one diastereomer (I) of either a tetrahydroquinoline or tetrahydroisoquinoline, as shown in Scheme IV, resulted in the equilibration of the diastereomer. No rearrangement was observed even under vigorous conditions, while forcing conditions resulted in decomposition.

The fact that this rearrangement is irreversible whereas the indolylindoline–benzodiazepine interconversion is an equilibrium process is explainable in terms of a structural prerequisite for ring opening. The indolylvinylpyrroloquinazoline structure D has lost fragment 8 as a structural feature and ring opening is not favored.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are corrected. Ir spectra were taken on either a Beckman Model IR 8 or IR 18A. NMR spectra were from a Varian A-60 or Varian XL-100 spectrometer. The mass spectra were obtained from either a CEC 21-104 or Varian MAT 311 mass spectrometer. Satisfactory analytical data were obtained on all of the compounds but are not all inclusive in the Experimental Section. Similar experimental procedures are given only for a representative of each class.

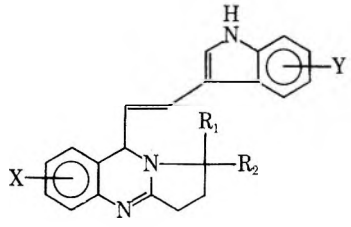
A. Pyrroloquinazoline Compounds (Table III). 1,1-Dimethyl-9-(3-indolylvinyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]benzo[*f*]quinazoline (10e). 3,4-Dihydro-4-(5,5-dimethyl-1-pyrrolin-2-yl)-3-indol-3-ylbenzo[*f*]quinoline hydrochloride[3] (**4e**, 3.0 g, 0.007 mol), 95% EtOH (250 ml), and 56% KOH solution (25 ml) were combined, stirred, and heated to reflux for 1 hr, when a white solid precipitated from the yellow solution. No starting material remained (tlc) and the reaction mixture was chilled and filtered, yielding a solid which gave 2 g (65% yield) of **10e**, mp 262–263.5° dec, upon recrystallization from EtOH.

B. Structure Correlation Compounds (Scheme II). 3-Indolylvinyl 2-Nitrophenyl Ketone (12). The procedure used was essentially that of Venturella, Bellino, and Piozzi.[8] A mixture of indole-3-carboxaldehyde (8.8 g, 0.06 mol), *o*-nitroacetophenone (10.0 g, 0.06 mol), piperidine (18 ml), and EtOH (115 ml) was refluxed for 2 hr, filtered hot, and then chilled to precipitate 10.7 g (61%, after drying at 80°) of **12**, mp 170–172°. Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.59. Found: C, 70.06; H, 4.03; N, 9.43; *m/e* 292 (M^+, $C_{17}H_{12}N_2O_3$ requires *m/e* 292).

3-[3-(2-Aminophenyl)-3-hydroxypropyl]indole (13). A solution of ketone **12** in EtOAc–HOAc was hydrogenated (50 psi) over PtO_2, filtered, concentrated, and recrystallized from isopropyl alcohol to give 3.2 g (61%) of 2′-amino-3-(3-indolyl)propiophenone, mp 165–167°. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.52; H, 6.02; N, 10.36. A hot stirred solution of this propiophenone (6.5 g, 0.025 mol, in 400 ml of isopropyl alcohol) was first treated portionwise with $NaBH_4$ (1.5 g, 0.033 mol), then refluxed for several hours, and finally chilled. The resulting solid was stirred in 100 ml of H_2O, filtered, and dried (80°) to give 4.0 g (61%) of **13**, mp 164.5–167°. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.62; H, 6.60; N, 10.55; *m/e* 266 (M^+, $C_{17}H_{18}N_2O$ requires *m/e* 266), 130 (100%, 3-indolyl-CH_2^+), 122 (52%, 2-NH_2^--benzyl alcohol).

9-(3-Indolylethyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (11). 1. A solution of 9-(3-indolylvinyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (**10a**, 0.63 g, 2 mmol) in 50 ml of HOAc was hydrogenated (50 psi) over PtO_2, filtered, and concentrated to an oil. After washing with benzene, the oil was precipitated in water and recrystallized twice from isopropyl alcohol to give 0.1 g (15%) of **11**, mp 236–239°. Anal. Calcd for $C_{21}H_{21}N_3$: C, 79.96; H, 6.71; N, 13.32. Found: C, 79.98; H, 6.74; N, 13.16; *m/e* 315 (M^+, $C_{21}H_{21}N_3$ requires *m/e* 315).

Table III
9-[1-(2-Indol-3-ylvinyl)]-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolines



Compd	X	Y	R_1	R_2	Mp, °C	Yield, %	Molecular formula	Analysis, % Calcd	Analysis, % Found
10a	H	H	H	H	228.5–232 dec (cor)	56.0	$C_{21}H_{19}N_3$	C, 80.48; H, 6.11; N, 13.41	C, 80.44; H, 5.84; N, 13.44
10b	H	H	H	CH_3	229.5–231.5 dec (cor)	13.5	$C_{22}H_{21}N_3$	C, 80.70; H, 6.47; N, 12.83	C, 80.76; H, 6.44; N, 13.00
10c	H	H	CH_3	CH_3	270–270.5 dec (cor)	79.6	$C_{23}H_{23}N_3$	C, 80.90; H, 6.79; N, 12.31	C, 81.13; H, 6.93; N, 12.15
10d	7-MeO	H	CH_3	CH_3	237.5–238.5 dec (cor)	50.8	$C_{24}H_{25}N_3O$	C, 77.60; H, 6.78; N, 11.31	C, 77.60; H, 6.56; N, 11.37
10e	7,8-Benzo	H	CH_3	CH_3	262–263.5 dec (cor)	64.8	$C_{27}H_{25}N_3$	C, 82.83; H, 6.44; N, 10.73	C, 82.94; H, 6.33; N, 10.89
10f	6-MeO	5-MeO	CH_3	H	207.5–209.5 (cor)	2.6	$C_{24}H_{24}N_3O_2$	C, 74.39; H, 6.50; N, 10.85	C, 74.67; H, 6.60; N, 10.92
10g	6-MeO	5-MeO	CH_3	CH_3	244.5–245.5 dec (cor)	72.4	$C_{25}H_{27}N_3O_2$	C, 74.78; H, 6.78; N, 10.47	C, 74.58; H, 6.83; N, 10.49

2. A solution of $POCl_3$ (0.8 g, 5 mmol, in 5 ml of $C_2H_4Cl_2$) was trickled into a stirred solution of **13** (1.4 g, 5 mmol) and 2-pyrrolidinone (0.45 g, 5 mmol) in 25 ml of $C_2H_4Cl_2$. After the initial exotherm subsided, the mixture was refluxed for several hours. The tarry reaction mixture was basified and the organic layer was removed and concentrated to a residual foam. The foam was extracted with benzene, dilution of which with hexane gave 0.5 g of a pink solid which was vacuum sublimed and recrystallized from benzene–hexane twice to give a small amount of solid which exhibited the same tlc behavior, ir, and mass spectrum as **11** prepared above in 1.

C. Rearrangement Rate Studies. Solutions for the rate studies were generally 5% (w/v). The sample tubes were kept in 75° oil baths and withdrawn periodically for NMR scan and returned to the bath. The shrinkage of the methyl peak of **4b** and its analogs and the growth of the methyl peak of **10b** and its analogs were the primary structural features used to evaluate relative concentrations. In certain instances, the methyl peaks of each diastereomer could be seen depending upon the experimental conditions.

Acknowledgment. The authors thank Professors R. M. Coates and R. A. Abramovitch for many helpful suggestions, and P. S. Schrecker and C. I. Kennedy for their contributions to structural analysis.

Registry No.—**4a**, 53089-20-6; **4b** isomer I, 53907-00-9; **4b** isomer II, 53907-01-0; **4c**, 53089-17-1; **4d**, 53907-02-1; **4e**, 53907-03-2; **4f**, 53907-04-3; **4g**, 53907-05-4; **10a**, 53907-06-5; **10b**, 53907-07-6; **10c**, 53907-08-7; **10d**, 53907-09-8; **10e**, 53907-10-1; **10f**, 53907-11-2; **10g**, 53907-12-3; **11**, 53907-13-4; **12**, 53907-14-5; **13**, 53907-15-6; 2′-amino-3-(3-indolyl)propiophenone, 53907-16-7.

References and Notes

(1) Presented at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 27, 1973.
(2) (a) Y. H. Wu, W. G. Lobeck, Jr., R. P. Ryan, and A. W. Gomoll, *J. Med. Chem.*, **15**, 529 (1972). (b) R. P. Ryan, W. G. Lobeck, Jr., C. M. Combs, and Y. H. Wu, *Tetrahedron*, **12**, 2325 (1971).
(3) R. P. Ryan, R. A. Hamby, and Y. H. Wu, *J. Org. Chem.*, **40**, 724 (1975).
(4) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, pp 812–813.
(5) B. G. Gower and E. Leete, *J. Am. Chem. Soc.*, **85**, 3683 (1963).
(6) The remaining bulk of the reaction material was polymeric in nature.
(7) Examination of models demonstrated the greater accessibility of the electron pair of attacking nitrogen when alkyl substituents on the nitrogen were "tied back" in a ring; cf. E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1959, p 278.
(8) P. Venturella, A. Bellino, and F. Piozzi, *Farmaco (Pavia)*, **26**, 591 (1971).

Syntheses of 4-Substituted Isoquinolines

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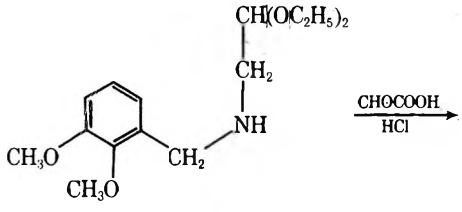
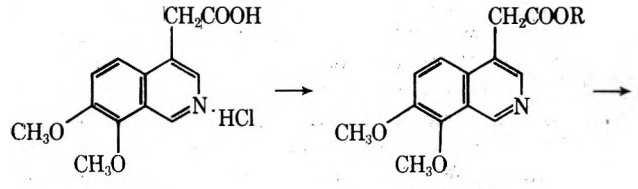
Received August 6, 1974

Several approaches to the synthesis of 4-substituted isoquinolines have been explored, as follows: preparation and α-alkylation of isoquinoline-4-acetic esters, alkylation of 3-cyanomeconin followed by ring expansion, α-alkylation and cyclization of o-carbomethoxyphenylacetonitrile, and oxidation of 4-hydroxy-1,2,3,4-tetrahydroisoquinoline to the oxo derivative with subsequent addition of a Grignard reagent. With the exception of the second, which was blocked at the last stage, all the methods were realized.

The work reported in this paper is presented as a contribution to the chemistry of 4-substituted isoquinolines, and especially to their syntheses, for which only a limited number of flexible methods are available.[1-3] The specific compounds were chosen with an eye to their structural relation with the benzophenanthridine alkaloids,[4] but the methods developed apply in general to 4-substituted isoquinolines. The approaches include: (1) alkylation of isoquinoline-4-acetic esters; (2) alkylation of a 3-cyanophthalide on its 3 position followed by ring expansion; and (3) alkylation of o-carbomethoxyphenylacetonitrile and cyclization to the corresponding homophthalimide. Also utilized was (4) Grignard addition to the carbonyl group of 4-oxo-1,2,3,4-tetrahydroisoquinoline, which could be prepared conveniently by oxidation of the readily accessible 4-hydroxy compound.

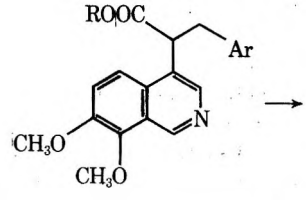


1

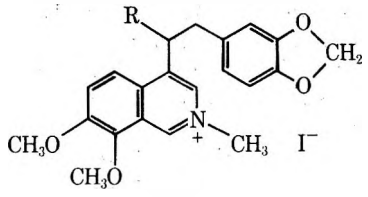


2

3, R = CH_3
4, R = C_2H_5

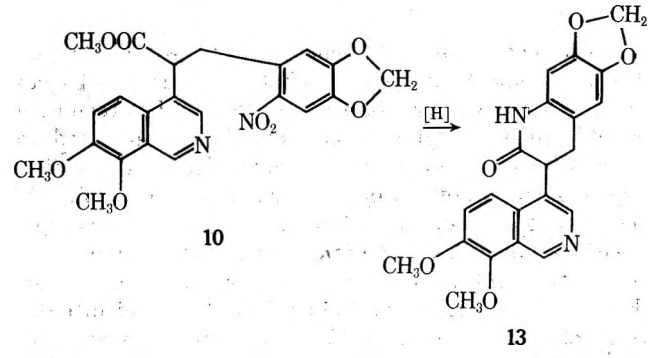


5, R = C_2H_5; Ar = 3′,4′-dimethoxyphenyl
6, R = CH_3; Ar = 3′,4′-dimethoxyphenyl
7, R = C_2H_5; Ar = phenyl
8, R = CH_3; Ar = 3′,4′-methylenedioxyphenyl
9, R = H; Ar = 3′,4′-methylenedioxyphenyl
10, R = CH_3; Ar = 3′,4′-methylenedioxy-6′-nitrophenyl



11, R = CO_2CH_3
12, R = CH_2OH

1. Alkylation of Isoquinoline-4-acetates. The elegant procedure of Bobbitt[1] was adapted to the preparation of isoquinoline-4-acetic acid **2** by allowing *N*-(2,3-dimethoxybenzyl)aminoacetal (**1**) to react with glyoxylic acid[5,6] in the presence of acid. The substituent at the 4 position of the corresponding esters **3** and **4** was elaborated by alkylating the ester enolates with benzyl chlorides. The yields of α-alkylation products **5–10** from the methyl ester (60–90%) were generally better than from the ethyl ester (30–35%). With variations possible in conditions, condensing base, and alkylating agent, this approach is adaptable to the synthesis of other kinds of 4-substituted isoquinolines. The methiodide **11** of the piperonyl derivative was reduced with lithium aluminum hydride both at the ester group and in the isoquinoline hetero ring; the product could be rearomatized directly to the quaternary alcohol salt **12**. No problem was encountered in the synthesis of nitro compound **10** despite exposure of the nitro group to strong base in liquid ammonia. However, when the nitro group in alkylation product **10** was reduced, cyclization could not be prevented, so that, instead of the amino compound, tetrahydroisoquinoline **13** was obtained.

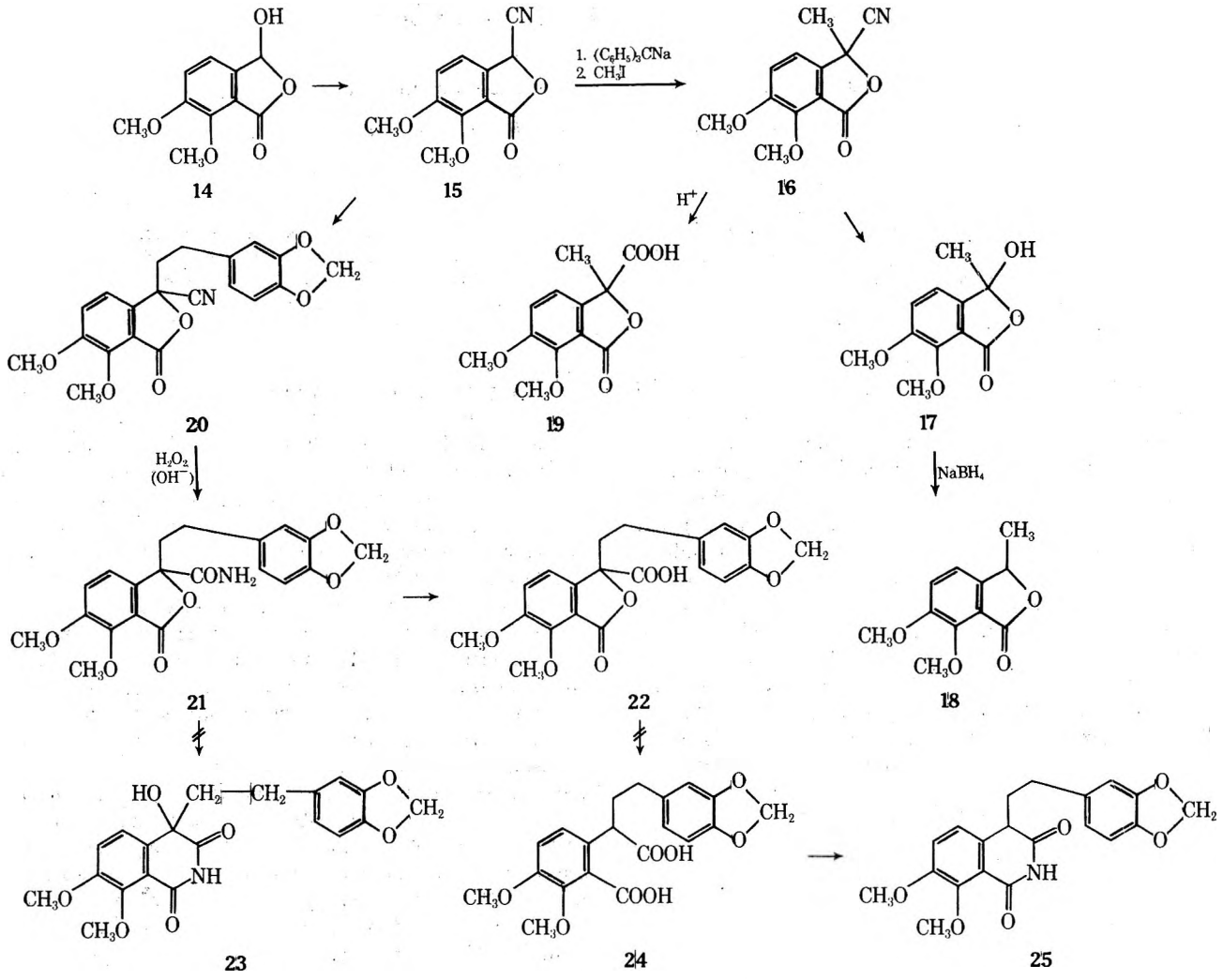


10

13

The acetic esters were hydrolyzed with exceptional ease to the corresponding acids, e.g., **8** to **9**. Since the acids are arylacetic acids, decarboxylation[7] appears quite feasible.

2. Alkylation of 3-Cyanomeconin (15). A second approach to the 4-substituted isoquinolines called for alkylation of the arylacetonitrile system, as in 3-cyano-6,7-dimethoxyphthalide (3-cyanomeconin, **15**), and conversion of the product, **20**, to the isoquinoline homophthalimide system, as in **23**. This series started with opianic acid (**14**), conveniently obtained from narcotine.[8] Cyanide ion reacts smoothly with opianic acid to give the necessary 3-cyanomeconin (**15**).[9] Methylation with the help of triphenylmethylsodium led to 3-cyano-3-methylmeconin (**16**), which on exposure to alkali lost cyanide ion. By reducing the resulting 3-methylopianic acid (**17**) to the known 3-methylmeconin (**18**),[10] the expected mode of alkylation on the 3 position was confirmed. When homopiperonyl iodide was substituted for methyl iodide in the alkylation step, 3-cyano-3-homopiperonylmeconin (**20**) was formed. Since di-



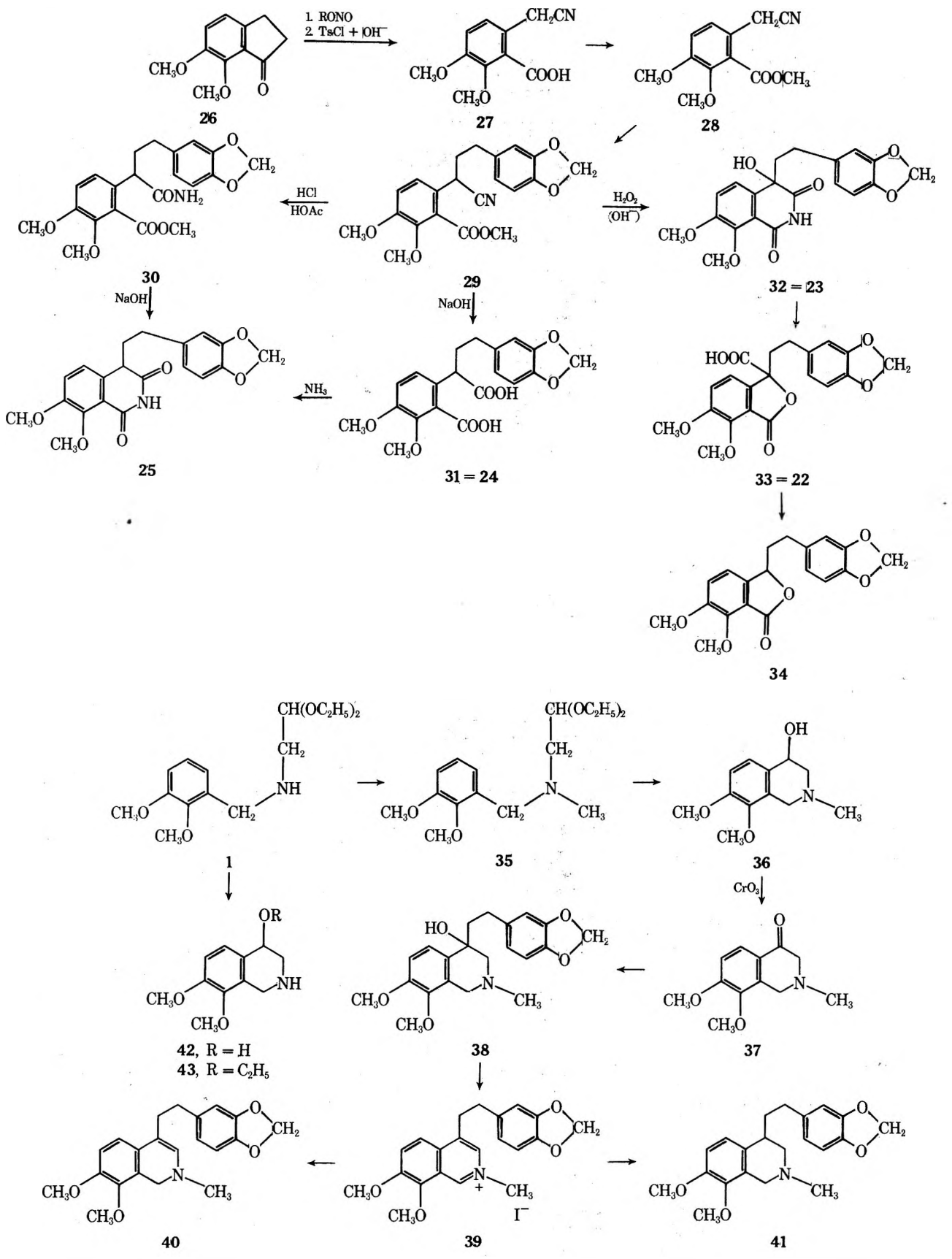
rect acid hydrolysis of **20** (analogous to **16** → **19**) failed, and direct alkaline hydrolysis eliminated the essential cyano group, a two-stage process was resorted to. Hydrogen peroxide with a catalytic amount of alkali[11] generated the amide **21**, which now could be safely hydrolyzed with alkali to 3-homopiperonylmeconin-3-carboxylic acid (**22**). This acid **22** was also obtained unexpectedly from α-homopiperonyl(2-carbomethoxy-3,4-dimethoxyphenyl)acetonitrile (**29**). Although the sequence broke down in its final stages, that is, in isomerizing phthalide **21** to **23**[12] and in reductively cleaving[13] phthalide **22** to homophthalic acid **24** (the intended precursor to homophthalimide **25**), we believe that this approach should not be lost sight of. So far as the reductive step **22** to **24** is concerned, cleavage of a benzyl-to-oxygen bond is involved, for which several alternate procedures are available.[13] For example, we have now confirmed the reported reduction of 6,7-dihydroxyphthalide-3-carboxylic acid to 3,4-dihydroxyhomophthalic acid with hydriodic acid.[14]

3. Alkylation of o-Carbomethoxyphenylacetonitrile. 2-Carboxy-3,4-dimethoxyphenylacetonitrile (**27**) is readily accessible by a two-step conversion from 6,7-dimethoxyindanone (**26**).[14] When sodium methoxide was used in the alkylation of the corresponding ester **28** with homopiperonyl iodide, the only products that could be identified were 7,8-dimethoxyhomophthalimide and 3,4-methylenedioxystyrene. Sodamide as condensing agent was more effective in furnishing the α-alkylation product **29**. Partial acid hydrolysis of **29** yielded the amide ester **30**, which under alkaline conditions cyclized to the desired 4-homopiperonyl-7,8-dimethoxyhomophthalimide (**25**).[15] The same homophthalimide **25** could be obtained also by hydrolyzing cyano ester **29** with alkali and cyclizing the resulting homophthalic acid **31** by heating it with ammonium carbonate.[15-17] Note that **31** is the same as **24**, so that the **24**-to-**25** step as projected before was realized here. Direct comparisons with a sample of 4-homopiperonyl-7,8-dimethoxyhomophthalimide synthesized elsewhere by a different route[15] confirmed the assigned structure of **25**.

When the Radziszewski hydrogen peroxide procedure[11] was applied to the cyano ester **29**, an oxidative step intruded, so that the product corresponded not to the expected amide ester **30**, but instead to 4-hydroxy-4-homopiperonyl-7,8-dimethoxyhomophthalimide (**32** or **23**). Hot aqueous alkali followed by acidification transformed 4-hydroxyhomophthalimide **32** to 3-homopiperonylmeconin-3-carboxylic acid (**33**), identical with the product **22** obtained before. Thermal decarboxylation to 3-homopiperonylmeconin (**34**) further confirmed the structure.

We have interpreted these transformations by postulating that hydrogen peroxide in the presence of a catalytic amount of alkali hydrolyzes cyano ester **29** readily to amide ester **30** in the usual way, and that in turn the amide ester with alkali cyclizes smoothly to 4-homopiperonyl-6,7-dimethoxyhomophthalimide (**25**). The enolate, readily formed by removal of hydrogen from the homophthalimide 4 position,[17] then oxidatively hydroxylates to yield the observed product **32**. Continued exposure of homophthalimide **32** to alkali would open the Py ring with loss of ammonia, and subsequent acidification would recyclize the intermediate hydroxyhomophthalic acid to phthalide **33**.

Since *o*-carbomethoxyphenylacetonitriles are smoothly



available from any indanone (cf. **26** to **27**), this alkylation–cyclization sequence provides a flexible approach to 4-substituted homophthalimides, which can then be modified in several ways.[17] If o-cyanophenylacetonitriles were generally accessible, they could serve equally as attractive starting materials.[18]

4. Oxidative Synthesis of 4-Oxotetrahydroisoquinoline Followed by Grignard Addition. Cyclization[1,5] of *N*-(2,3-dimethoxybenzyl)-*N*-methylaminoacetal (**35**) with acid produced 2-methyl-4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**36**) in high yield. After conditions were found for controlled oxidation at the 4-hydroxyl group, the 4-keto compound **37** became available, and this with homopiperonylmagnesium bromide gave rise to the desired 2-methyl-4-hydroxy-4-homopiperonyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**38**). Dehydration and

1

Experimental Section

General. - Nuclear magnetic resonance spectra were determined at 60 MHz. Our thin-layer chromatograms utilized woven glass plates impregnated with silica gel (Gelman Type SG) as well as glass plates (Eastman 301R); they were developed with a spray of 1:1 sulfuric acid in ether or by exposure to iodine vapor. Analyses for elements were reported by the Microchemical Laboratories at Massachusetts Institute of Technology, Scandinavian Microanalytical Laboratory in Herlev, Denmark, Spang Microanalytical Laboratory in Ann Arbor, Michigan, Galbraith Laboratories in Knoxville, Tennessee, K. Ritter at Analytisches Laboratorium in Basel, and by C.K. Fitz, Needham Heights, Massachusetts (who reported percentage compositions to the tenth's place).

(7,8-Dimethoxyisoquinolyl-1)-acetic Acid (2). - 2,3-Dimethoxybenzylaminoacetal[5] (7.1 g; 25 mmol) in 50 ml of concentrated hydrochloric acid plus 50 ml of alcohol, was mixed with a solution of 40% aqueous glyoxylic acid (7.4 g containing 25 mmol) in 50 ml of alcohol. After refluxing the mixture 0.5 - 1 hr, it was evaporated under reduced pressures at 100°. Rubbing the almost dry residue with 3:1 alcohol-ether furnished needles, which were crystallized twice from ethanol to give the yellow needle-like hydrochloride of (7,8-dimethoxyisoquinolyl-4)-acetic acid (2), mp 178-181°, in 93% yield. Material melting at 194-195° (decomp.) could be obtained by crystallization from 2N hydrochloric acid. The hydrochloride showed a bright fluorescence under ultraviolet light; uv max (1.7×10^{-5} M in C_2H_5OH) 236 nm (log ε 4.57), 252 sh (4.22), 286 (3.64); ir (mineral oil mull) 1705 cm^{-1}; nmr (D_2O) δ 9.54 (s, 1, H-1), 8.35 (s, 1, H-3), 7.99 (s, 2, H-5,6), 4.30 (s, 2, CH_2), 4.08 ppm (s, 6, 2-CH_3O); nmr (F_3CCOOH) δ 9.81 (broad s, 1, H-1); 8.46 (broad s, 1, H-3), 8.18 (s, 2, H-5,6), 4.45 (s, 2, CH_2), 4.37 and 4.20 ppm (s's, 6, 2CH_3O). The spectra were not examined beyond δ 10 ppm.

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Anal. Calcd. for $C_{13}H_{15}ClNO_4$: C, 55.00; H, 4.97; N, 4.97. Found: C, 54.87; H, 4.92; N, 5.25.

Methyl (7,8-Dimethoxyisoquinolyl-4)-acetate (3). - Thionyl chloride (6 ml) was added dropwise to a stirred suspension (-5°) of 2.8 g (10 mmol) of (7,8-dimethoxyisoquinolyl-4)-acetic acid hydrochloride in 20 ml of absolute methanol. After 15 min at -5°, the solution was stirred at room temperature for 3 hr, and then stripped of solvent at ca. 40°. Adding acetone to the gummy residue gave rise to solids, which on two crystallizations from ethanol or methanol afforded the highly fluorescent, yellow, crystalline hydrochloride of methyl (7,8-dimethoxyisoquinolyl-4)-acetate (3), mp 181-183°, in 84% yield; uv max (3×10^{-5} M in ab C_2H_5OH) 236 nm (log ε 4.48), 252 (4.34), 288 (3.56); ir (mineral oil mull) 1745 cm^{-1}; nmr (D_2O) δ 9.57 (s, 1, H-1), 8.33 (s, 1, H-3), 7.98 (q, J=9,1.5, 9 Hz, 2, H-5,6) 4.30 (s, 2, CH_2), 4.07 (s, 6, 7,8-diCH$_3$O), 3.78 ppm (s, 3, $COOCH_3$); nmr (F_3CCOOH) δ 10.05 (broad s, 1, H-1), 8.61 (broad s, 1, H-3), 8.25 (s, 2, H-5,6), 4.42 (s, 2, CH_2), 4.37 and 4.21 (s's, 6, 7,8-diCH$_3$O), 3.96 ppm (s, 3, $COOCH_3$).

Anal. Calcd. for $C_{14}H_{16}ClNO_4$: C, 56.47; H, 5.42; N, 4.71. Found: C, 56.74; H, 5.30; N, 4.46.

The picrate of methyl (7,8dimethoxyisoquinolyl-4)-acetate (3), precipitated from a saturated solution of picric acid in 95% ethanol, showed mp 182-184°.

Anal. Calcd. for $C_{20}H_{18}N_4O_{11}$: C, 60.29; H, 4.56; N, 16.08. Found: C, 60.00; H, 4.44; N, 15.97.

The free base 3 was released from its hydrochloride (2 g) by shaking the hydrochloride with sodium bicarbonate in 30 ml of methanol-water. The base was extracted into chloroform, and the extract was dried and stripped of solvent at room temperature. Methyl (7,8-dimethoxyisoquinolyl-4)-acetate (3) was obtained with mp 64-66° in 55% yield by recrystallizing the residue from a small volume of water; uv max (4×10^{-5} M in C_2H_5OH) 236 nm (log ε 4.63), 282 sh (3.80), 290 sh (3.78), 349 (3.88); ir ($CHCl_3$) 1740 cm^{-1}; nmr (CCl_4) δ 9.31 (s, 1, H-1), 8.16 (s, 1, H-3), 7.44 (q, J=9.4,9 Hz, 2, H-5,6), 3.98 and 3.88 (s's, 6, 7,8-diCH$_3$O), 3.79 (s, 2, CH_2), 3.55 ppm (s, 3, $COOCH_3$); nmr (F_3CCOOH) δ 9.66 (broad s, 1, H-1), 8.26 (broad s, 1, H-3), 8.12 (s, 2, H-5,6), 4.40 (s, 2, CH_2), 4.35 and 4.19 (s's, 6, di-CH_3O), 3.95 ppm (s, 3, $COOCH_3$).

3

Ethyl (7,8-Dimethoxyisoquinolyl-4-)-acetate (4). - The hydrochloride of this ester 4 was prepared from the hydrochloride of acid 2 by using ethanol in place of methanol in the above procedure. Recrystallization from methanol gave the crystalline salt (81%) with mp 160-163°; ir (mineral oil mull) 1735 cm^{-1}; nmr (D_2O) δ 9.44 (s, 1, H-1), 8.26 (s, 1, H-3), 7.83 (q, J=9,4, and 9 Hz, 2, H-5,6), 4.17 (s, CH_2), 4.01 (m, CH_2CH_3), 3.95 (s, 6, 7,8-diCH$_3$O), 1.17 ppm (t, J=9 Hz, 3, CH_2CH_3). Integration at δ 4.17 and 4.01 ppm indicated 4 protons.

The free base of ethyl (7,8-dimethoxyisoquinolyl-)acetate (4) was recrystallized from water to give crystals, mp 80-81°; ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 9.44 (s, 1, H-1), 8.21 (s, 1, H-3), 7.47 (q, J=9,5,9 Hz, 2, H-5,6), 4.11 (q, J=7 Hz, CH_2CH_3), 4.00 and 3.92 (s's, 7,8-di-CH_3O), 3.82 (s, CH_2), 1.25 ppm (t, J=7 Hz, 3, CH_2CH_3). Integration of the 4.11-3.82 signals corresponded to 10 protons as required.

The free base was converted to its picrate, mp 171-172°, for analysis.

Anal. Calcd. for $C_{23}H_{26}N_4O_{11}$: C, 50.01; H, 4.00; N, 11.11. Found: C, 49.96; H, 4.07; N, 11.29.

Ethyl α-(7,8-Dimethoxyisoquinolyl-4)-α-veratrylacetate (5). - Crystals of ethyl (7,8-dimethoxyisoquinolyl-4-)acetate hydrochloride (4) (3.1 g; 10 mmol) were added in small portions to a stirred refluxing mixture of commercial sodamide (1.7 g; 43 mmol) in 500 ml of liquid ammonia that had been condensed directly into the reaction flask. The resulting red solution was stirred for 15 min before adding veratryl chloride (1.9 g; 10 mmol) and stirring further for 1-2 hr. Ammonium chloride (2.5 g; 50 mmol) was added in portions, after which the ammonia was allowed to evaporate.

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The residual solid was triturated with anhydrous acetone (50 ml), and acetone-insoluble material was discarded. The solution was dried and evaporated, and the remaining brown oil was dissolved in 25 ml of absolute ethanol. Adding drops of a saturated alcohol solution of picric acid gave a bright yellow precipitate, which was recrystallized from absolute ethanol to obtain the picrate of ethyl α-(7,8-dimethoxyisoquinolyl-4)-α-veratrylacetate (5), mp 120-130°, in 60% yield; ir ($CHCl_3$) 1735 cm^{-1}; nmr ($CDCl_3$) δ 9.22 (s, 1, H-1), 8.97 (s, 2, picrate Ar H's), 8.53 (s, 1, H-3), 7.98 (q, J=7,2,7 Hz, 2, H-5,6), 6.72 (s, 3, veratryl Ar H's), 4.26 and 4.12 (s's, 7,8-diCH$_3$O),4.0 (m, CH_2CH plus $COOCH_3$), 3.84 (s, veratryl CH$_3$O's), 1.23 ppm (t, J=7.5 Hz, 3, CH_2CH_3). The δ 4.26 - 3.84 ppm signals together corresponded to 17 protons.

Anal. Calcd. for $C_{30}H_{30}N_4O_{13}$: C, 55.04; H, 4.62. Found: C, 54.81; H, 4.85.

Methyl α-(7,8-Dimethoxyisoquinolyl-4)-α-veratryl acetate (6). - Alkylation of the methyl ester 3 with veratryl chloride was performed essentially the same as with the ethyl ester. The twice-crystallized picrate of methyl α-(7,8-dimethoxyisoquinolyl-4)-α-veratrylacetate, (6), mp 163.5-165°, was obtained in 35% yield; ir ($CHCl_3$) 1735 cm^{-1}; nmr ($CDCl_3$) δ 9.68 (s, 1, H-1), 8.90 (s, 2, picrate Ar H's), 8.55 (s, 1, H-3), 7.98 (s, 2, H-5,6), 6.68 (s, 3, veratryl Ar H's), 4.18 and 4.08 (s's, 6, 7,8-diCH$_3$O), 3.90 (m, 3, CH_2CH), 3.79 (s, 6, veratryl CH$_3$O's), 3.70 ppm (s, 3, $COOCH_3$).

None of the following showed signs of forming the enolate from methyl (7,8-dimethoxyisoquinolyl-4)acetate (3): triphenylmethyllithium, sodium hydride in dimethoxyethane, sodamide in boiling benzene, or sodium hydride in hexamethylphosphoramide.

Ethyl α-(7,8-Dimethoxyisoquinolyl-4)-α-benzylacetate (7). - The alkylation procedure was much the same as before, except that benzyl chloride was used. The picrate of ethyl α-(7,8-dimethoxisoquinolyl-4)-α-acetate (7) was obtained after three crystallizations from alcohol as yellow crystals (30%) mp 153-155°.

5

Anal. Calcd. for $C_{28}H_{28}N_4O_{11}$: C, 56.56; H, 4.41; N, 9.42. Found: C, 56.74; H, 4.70; N, 9.15.

The free base 7 could be obtained as an oil showing only a single spot on thin-layer chromatography (30-60° petroleum ether-ether, 1:4); nmr (CCl_4) δ 9.30 (s, 1, H-1), 8.28 (s, 1, H-3), 7.49 (q, J=11,14,11 Hz, 2, H-5,6), 7.02 (s, 5, phenyl Ar H's), 4.31 (m, 1, H-C-COO), 3.91 and 3.78 (s's, 6, 7,8-diCH$_3$O), 3.35 (m, 4, ArCH$_2$-C-CH$_2$), 0.96 ppm (t, J=7.5 Hz, 3, CH_2CH_3).

Methyl α-(7,8-Dimethoxyisoquinolyl-4)-α-piperonylacetate (8) and Its Methiodide (11). - Piperonyl chloride[21] was prepared by stirring a mixture of piperonyl alcohol (15.2 g; 0.10 mol), thionyl chloride (14 g; 0.11 mol) and solid sodium bicarbonate (14.4 g; 0.11 mol) in 100 ml of dry benzene for 2 hr at room temperatures. Filtration and distillation gave piperonyl chloride (13.2 g; 76%) with b.p 78-80° (0.05 mm).

The hydrochloride of methyl (7,8-dimethoxyisoquinolyl-4)-acetate (3) (2.0 g; 6.6 mmol) was allowed to react as above first with sodamide (1.0 g; 2.5 mmol) in 500 ml of liquid ammonia and then with piperonyl chloride (1.1 g; 6.6 mmol). After a 2-hr reaction period, 5.8 g (110 mmol) of ammonium chloride was added, after which the alkylation product, methyl α-(7,8-dimethoxyisoquinolyl-4)-α-piperonylacetate (8), was isolated as a yellow glass by the procedure described above.

A small sample, brought out of ethanol-ether, afforded crystalline material, mp 142-143°; nmr (CCl_4) δ 9.36 (s, 1, H-1), 8.28 (s, 1, H-3), 7.55 (q, J=9,11.9 Hz, 2, H-5,6), 6.55 (s, 3, piperonyl Ar H's), 5.83 (s, 2, $CH_2(O)_2$), 4.00 and 3.91 (s's, 7,8-diCH$_3$O), 3.54 (m, $CHCH_3$), 3.52 ppm (s, CH_2OOC). Integration of the δ 4.0-3.52 ppm signals indicated 12 H's.

Another portion in solution with benzene was treated with hydrogen chloride. Recrystallization of the resulting gum from 95% ethanol gave the crystalline hydrochloride of methyl α-(7,8-dimethoxyisoquinolyl-4)-α-piperonylacetate, homogeneous according to thin-layer chromatography and showing mp 130-132°; nmr ($CDCl_3$) δ 9.70 (s, 1, H-1), 8.95 (s, 1, H-3), 8.15 (s, 2, H-5,6), 6.68 (m, 3, piperonyl Ar H's), 5.96 (s, 2, $CH_2(O)_2$), 4.7-2.9 (m, CH_2CH), 4.23 and 4.18 (s's, 7,8-diCH$_3$O), 3.70 ppm (s, CH_3OOC). The last three signals corresponded to 12 protons.

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The bulk of the yellow glassy product was dissolved in dry benzene, methyl iodide (10 ml) was added, and the solution was stirred in a nitrogen atmosphere for 3 hr. The yellow hygroscopic precipitate was collected and washed repeatedly with benzene to give 3.2 g (91% from 3) of the desired methiodide of methyl α-(7,8-dimethoxyisoquinolyl-4)-α-piperonylacetate (11), mp 101-103°. Recrystallization from alcohol did not change the melting point. This material showed one spot on thin-layer chromatogrpahy (4:1 benzene-ethanol); uv max (2×10^{-5} M in ab C_2H_5OH) 216 nm (log ε 4.59), 257 (4.6), 288 (3.84); ir ($CHCl_3$) 1725, 1645, 1620, 1575 cm^{-1}; nmr ($CDCl_3$) δ 10.00 (s, 1, H-1), 8.51 (s, 1, H-3), 7.96 (s, 2, H-5,6), 6.68 (s, piperonyl H-6'), 6.58 (s, piperonyl H-2',5'), 5.83 (s, 2, $CH_2(O)_2$), 4.76 (s, $CH_3\overset{+}{N}$), 4.57 (m, $\underset{I}{H}COOCH_3$), 4.28 and 4.08 (s's, 6, 7,8-diCH$_3$O), 3.63 (s, $COOCH_3$), 3.40 ppm (m, piperonyl CH_2). Integration between δ 6.68-6.58 ppm corresponded to 3 protons, between 4.76-4.57 to 4 protons, and between 3.63-3.40 to 5 protons.

Anal. Calcd. for $C_{23}H_{24}INO_6$: C, 51.41; H, 4.50; N, 2.61. Found: C, 51.50; H, 4.56; N, 2.81.

α-(7,8-Dimethoxyisoquinolyl-4)-α-piperonylacetic Acid (9) from Its Methyl Ester 8. - Methyl α-(7,8-dimethoxyisoquinolyl)-α-piperonylacetate (8) was stirred for 1 hr at room temperature with 10% hydrochloric acid, after which period volatiles were removed under reduced pressures (100°). Two crystallizations of the residue from small volumes of ethanol afforded white crystals of α-(7,8-dimethoxyisoquinolyl-4)-α-piperonylacetic acid hydrochloride (9), mp 183-185°, in 80% yield; uv max (3×10^{-5} M in C_2H_5OH) 236 nm (log ε 4.45), 253 (4.30), 286 (3.78);

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ir (mineral oil mull) 1720, 2450 cm^{-1}; nmr (F_3CCOOH) δ 9.74 (s, 1, H-1), 8.43 (s, 1, H-3), 8.06 (s, 2, H-5,6), 6.54 (s, 3, piperonyl Ar H's), 5.73 (s, 2, $CH_2(O)_2$), 4.93 (t, J=10 Hz, 1, $\underset{I}{H}COOH$), 4.23 and 4.13 (s's, 6, 7,8-diCH$_3$O), 3.53 ppm (m, 2, Ar$\underset{I}{CH}_2$).

Anal. Calcd. for $C_{21}H_{21}ClNO_6$: C, 60.36; H, 4.82; N, 3.35. Found: C, 60.13; H, 4.88; N, 3.55.

Methiodide of β-(7,8-Dimethoxyisoquinolyl-4)-β-piperonyl-ethanol (12). - Lithium aluminum hydride (0.3 g; 8 mmol) was added to a stirred, ice-cold solution of the methiodide of methyl α-(7,8-dimethoxyisoquinolyl-4)-α-piperonylacetate (11) (0.50 g; 0.93 mmol) in 150 ml of tetrahydrofuran that had been dried with calcium hydride. Nitrogen covered the reaction mixture. The mixture was stirred for various periods (1 min - 1 day) at various temperatures (0°-30°) without significant difference in the results. Small portions of ice were introduced until no further bubbling was noted. After drying ($MgSO_4$), the mixture was filtered through diatomaceous earth, and the filtrate was stripped of solvent.

A portion (0.10 g; 0.25 mmol) of the residual frothy glass in 3 ml of methanol and 10 ml of 95% alcohol was refluxed for 6 hr with 0.20 g (0.79 mmol) of iodine and 0.40 g (4.2 mmol) of anhydrous potassium acetate. Then aqueous 6.7% sulfurous acid was added at room temperature until the red color changed to bright yellow-orange. Volatiles were removed (50° bath; reduced pressure), the remaining dry solid was thoroughly extracted with chloroform, and the chloroform-soluble material was recrystallized from 1:1 methanol-ether and from methanol to give the yellow methiodide of β-(7,8-dimethoxyisoquinolyl-4)-β-piperonyl-ethanol (12), mp 190-192°, in about 50% yield. This product showed a single spot on thin-layer chormatography (4:1 benzene-ethanol); uv max (4×10^{-5} (4×10^{-5} M in ab C_2H_5OH) 230 nm (log ε 4.34), 256 (4.06), 287 (3.86); ir ($CHCl_3$) 2470, 1650 (C=N) cm^{-1}; nmr ($CDCl_3$) δ 9.48 (s, 1, H-1), 8.49 (s, 1, H-3), 7.94 (q, J=8,5,8 Hz, 2, H-5,6), 6.66 and 6.60 (s's, 3, piperonyl Ar H's), 5.84

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(s, 2, $CH_2(O)_2$), 4.64 (s, 3, $CH_3\overset{+}{N}$), 4.17 and 4.05 (s's, 6, 7,8-diCH$_3$O), 3.94 (m, 3, piperonyl-$\underset{I}{CH}_2\underset{I}{CH}$), 3.07 ppm (m, 3, $\underset{I}{CH}_2\underset{I}{OH}$).

Anal. Calcd. for $C_{21}H_{24}INO_5$: C, 51.88; H, 4.76; N, 2.75. Found: C, 52.03; H, 5.06; N, 2.83.

Methyl α-(7,8-Dimethoxyisoquinolyl-4)-α-(6'-nitropiperonyl)-acetate (10). - 6-Nitropiperonyl chloride was prepared by adding piperonyl chloride (18.1 g) in portions to concentrated nitric acid (200 ml) at -15°. The mixture was then stirred for 2 hr at -10° and for 2 hr at room temperature. The reaction mixture was poured into a liter of water, and the solids were collected. After processing, recrystallized 6-nitropiperonyl chloride (8.6 g) was obtained with mp 78-80° [lit.[22] 83; 86°]. Another preparation gave light orange leaflets, mp 82-84°.

Anal. Calcd. for $C_8H_6ClNO_4$: C, 44.57; H, 2.80. Found: C, 44.67; H, 2.76.

According to the alkylation described above, 2.0 g (6.6 mmol) of methyl (7,8-dimethoxyisoquinolyl-4)-acetate hydrochloride (3) in liquid ammonia containing 0.4 g of sodamide (10 mmol) was combined with 1.5 g (6.6 mmol) of 6-nitropiperonyl chloride. Recrystallization of the crude product from methanol yielded faintly yellow methyl α-(7,8-dimethoxyisoquinolyl-4)-α-(6'-nitropiperonyl)-acetate (10), mp 150-151°, in 65% yield. This material showed one spot on thin-layer chromatography (chloroform); ir ($CHCl_3$) 1735, 1565, 1335, 875 cm^{-1}; nmr ($CDCl_3$) δ 9.31 (s, 1, H-1), 8.26 (s, 1, H-3), 7.32 (s, H-5'), 7.52 (q, J=9,12,9 Hz, H-5,6), 6.38 (s, 1, H-2'), 5.84 (s, 2, $CH_2(O)_2$), 4.53 (t, J=7 Hz, 1, $\underset{I}{H}COOCH_3$), 3.93 and 3.74 (s's, 6, 7,8 diCH$_3$O), 3.45 (m, piperonyl CH_2), 3.42 ppm (s, $COOCH_3$). The integration from 7.32 and 7.52 indicated 3 H's, and from 3.45 and 3.42, 5 H's.

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product. Sodium hydride in hexamethylphosphoramide gave only recovered ester 3, whereas triphenylmethyllithium in tetrahydrofuran allowed recovery of both reactants.

Alkylation in boiling benzene with or without sodamide resulted in substitution on nitrogen instead of carbon. The yellow crystals of the quaternary chloride (43%) obtained out of ether-ethanol with mp 174-175° (decomp), were homogeneous according to thin-layer chromatography ($CHCl_3$-CH_3OH, 9:1); ir (mineral oil mull) 1725, 1520, 1330 cm^{-1}; nmr (F_3CCOOH) δ 9.22 (broad s, 1, H-1), 7.72 (d, J=5 Hz, 1, H-3), 7.50 (d, J=5 Hz, 2, $CH_2\overset{+}{N}$), 7.23 (s, 1, H-5'), 6.53 (s, 1, H-2'), 5.67 (s, $CH_2(O)_2$), 5.60 (broad s, together with preceding signal 4, H-5,6), 3.70 (m, 5, $\underset{I}{CH}_2COOCH_3$ plus $ArOCH_3$), 3.58 (s, 3, $ArOCH_3$), 3.10 ppm (s, 3, $COOCH_3$).

Anal. Calcd. for $C_{22}H_{21}\overset{Cl}{\underset{I}{N}}_2O_8$: C, 54.42; H, 4.44; Cl, 7.44; N, 5.88. Found: C, 54.60; H, 4.32; Cl, 7.61; N, 5.90.

Reduction and Cyclization of Nitro Compound 10 to 13. - A mixture of 0.60 g (1.3 mmol) of methyl α-(7,8-dimethoxyisoquinolyl-4)-α-(6'-nitropiperonyl)-acetate (10) and prereduced platinum oxide catalyst (0.1 g) in 35 ml of ethanol was stirred under hydrogen for approximately 3 hr, at which time 115% of the calculated 3 molar equivalents of hydrogen had been absorbed. Removal of catalyst and of all solvent (T below 40°) left a white residue, which was brought out of methanol to give colorless crystals of 2-oxo-3-(7',8'-dimethoxyisoquinolyl-4')-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (13), mp 281-283°, in 59% yield; uv max (3×10^{-5} M ab C_2H_5OH) 213 nm (log ε 4.18), 236 (4.13), 278 sh; ir (mineral oil mull) 1680, 3220 cm^{-1}; nmr (F_3CCOOH) δ 9.51 (broad s, H-1'), 8.10 (broad s, H-3'), 7.98 (s, H-5',6') with the last 3 signals integrating to 3H's, 6.55 and 6.51 (s's, 2, H-5,8), 5.81 (s, 2, $CH_2(O)_2$), 4.77 (m, 1, H-3), 4.15 and 4.00 (s's, 6, 7',8'-diCH$_3$O), 3.28 ppm (m, 2, H-4).

Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.67; H, 4.79; N, 7.40. Found: C, 66.83; H, 4.90; N, 7.26.

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Reduction of 10 with tin and hydrochloric acid at 0° gave the same product 13 and offered no advantages.

Opianic Acid (14) from Narcotine. - The procedure described here is a considerably improved version of the reaction originally reported by Matthiessen and Foster.[8] A mixture of narcotine (225 g; 0.55 mol), manganese dioxide (203 g; 2.33 mol), and 3375 ml of 10% sulfuric acid was refluxed for 2.5 hrs. The hot mixture was filtered, the filtrate was cooled overnight, and the precipitated opianic acid (14) was collected, washed with cold water, and air-dried. Decolorization with charcoal followed by crystallization from 1.5 l. of water gave 85 g (75%) of cream-colored opianic acid (14), mp 145-146° [lit.[23], 142-146°].

3-Cyanomeconin (15) from Opianic Acid (14).[9] - Combining 42 g of opianic acid with potassium cyanide gave 3-cyanomeconin (15), mp 100-101°, in 70% yield, and twice-crystallized product, mp 102-103°, in 52% yield [lit.[9], mp 103-104].

3-Cyano-3-methylmeconin (16) by Methylation of 3-Cyanomeconin (15). - The methylation was performed in a manner similar to that described below for the homopiperonyl alkylation, except that the ether solvent was not replaced with benzene. An ether solution of 3-cyanomeconin (10 mmol) developed a permanent blood-red color only at the very end of the addition of ethereal triphenylmethylsodium[24] (122 ml containing 10 mmol). Methyl iodide in about 6-fold excess was introduced, and the mixture was allowed to stand at room temperature. Titration of aliquots showed that 93% of the base had disappeared after 18 hr, and that a total of 97% had disappeared after an additional 2 hr of reflux. 3-Cyano-3-methylmeconin (15) crystallized once from alcohol-water was obtained as a faintly yellow solid (1.6 g; 67%), mp 130-132.° Recrystallizations afforded colorless product, mp 134.5-135°.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 61.80; H, 4.75. Found: C, 61.7; H, 4.8.

3-Methylmeconin (18) from 3-Cyano-3-Methylmeconin (16). - 3-Cyano-3-methylmeconin (0.1 g) was warmed on a steambath for 12 min with 2.5 ml of 8% aqueous

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sodium hydroxide. Acidification evolved HCN, and cooling gave a precipitate, which after one crystallization from water weighed 35 mg; mp 134-145°; mixture melting point with the starting material, 110-129°.

The crystals, taken as 3-methyl-3-hydroxymeconin (17), were allowed to stand for 3 hr with a solution of sodium borohydride (70 mg) in absolute ethanol (7 ml). Solvent was removed, hydrochloric acid was added, and the mixture was heated a short time on the steambath before chilling. The precipitate on crystallization from water furnished white glittering needles of 3-methylmeconin, mp 98-98.5°. [lit.[10], mp 101°]; ir max 1749 cm^{-1}.

Omitting alkali, and instead exposing 3-methyl-3-cyanomeconin directly to 25% hydrochloric acid on the steambath for 1 hr gave 3-methylmeconin-3-carboxylic acid (19) in 95% yield. On recrystallization from water, this acid showed mp 196.5-197° (effervescence).

Anal. Calcd. for $C_{13}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.4; H, 4.8.

Homopiperonyl Bromide and Iodide. - Phosphorous tribromide (10.2 g; 38 mmol) was added dropwise to a cold solution of homopiperonyl alcohol (15 g; 91 mmol) in 120 ml of benzene. The mixture was stirred at ice bath temperature for 0.5 hr, then refluxed for 1 hr, and finally allowed to stand overnight at room temperature. The reaction mixture was quenched over cracked ice, and the aqueous layer was extracted with ether. The combined organic phases were shaken with dilute carbonate solution, and with water, before drying over magnesium sulfate. Fractional distillation gave 8.6 g (83%) of homopiperonyl bromide, bp 129-131° (1.5 mm) or 97-100° (0.2 mm); n_D^{25} 1.573.

Anal. Calcd. for $C_8H_7BrO_2$: C, 47.30; H, 3.96. Found: C, 47.2; H, 4.0.

The quaternary salt derivative, N-homopiperonyl-pyridinium bromide, formed readily by warming the bromide in pyridine, showed mp 244.5-245° (decompose).

Anal.Calcd. for $C_{14}H_{14}BrNO_2$: C, 54.55; H, 4.58. Found: C, 54.6; H, 4.8.

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Crude dry homopiperonyl bromide obtained from 15 g of the alcohol was dissolved in 425 ml of acetone containing 27 g of sodium iodide. After 1 day at reflux temperature, solvent was removed, and the residue was extracted into ether. The ether-soluble material was crystallized from ethanol-water to get 19.5 g (78% from the alcohol) of colorless homopiperonyl iodide, mp 36-37°. The sample for analysis showed mp 40.1-40.4°.

Anal. Calcd. for $C_8H_7IO_2$: C, 38.73; H, 3.25. Found: C, 38.8; H, 3.3.

N-Homopiperonylpyridinium Iodide, obtained from ethanol as glistening white crystals, melted at 205-206°.

Anal. Calc. for $C_{14}H_{14}INO_2$: C, 47.33; H, 3.97. Found: C, 47.7; H, 4.1.

3-Cyano-3-homopiperonylmeconin (20) by Alkylation of 3-Cyanomeconin (15). - The apparatus used here was scrupulously dry, and a current of dry nitrogen was maintained over the reaction mixtures throughout the reaction. Ether was distilled from lithium aluminum hydride and condensed directly onto 2.2 g (10 mmol) of 3-cyanomeconin (15). The resulting mixtures was titrated with ethereal triphenylmethylsodium[24] (ca. 0.1 M) until the red color persisted. Then over the course of 0.5 hr homopiperonyl iodide (6.2 g; 22 mmol) in a Soxhlet unit was extracted with ether directly into the boiling reaction mixture. Solvent was exchanged by condensing dry benzene vapors directly into the reaction vessel while distilling ether out. When the boiling point reached 80°, the resulting benzene solution (ca. 200 ml) was refluxed for 1 day.

Aqueous 2% acetic acid (100 ml) was added with cooling, and the aqueous layer was extracted with ether and benzene. The combined organic layers were rinsed with small portions of water, dried, and then warmed in a jet of clean nitrogen to remove solvent. After rinsing the slushy residue several times with 30-60° petroleum ether to remove triphenylmethane and unchanged homopiperonyl iodide, the remaining gum was recrystallized (charcoal) from 95% alcohol to give fine cream-colored crystals (0.89 g or 24%) of 3-cyano-3-homopiperonylmeconin

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(20), mp 144.5-145.5°; further recrystallizations brought this value to 146-146.5°.

Anal. Calcd. for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66. Found: C, 65.3; H, 4.7.

Processing the petroleum ether triturate afforded 2.1 g of unchanged homopiperonyl iodide or 70% of the excess. Approximately the same yield of alkylation product was obtained when the iodide was taken in equimolecular amounts. However, if ether alone was used as reaction solvent, the yield was 8%. The reaction with homopiperonyl bromide in place of the iodide was unsatisfactory in ether but was not tried in benzene solvent. When benzene suspensions of sodamide, sodium hydride, or sodium (dispension) were used instead of ethereal triphenylmethylsodium, no reaction occured.

3-Homopiperonylmeconin-3-carboxamide 21. - Hydrogen peroxide (25 ml of 10% aqueous solution) plus 2 ml of 10% sodium hydroxide was added to a stirred suspension of 4.0 g of 3-cyano-3-homopiperonylmeconin (20) in 25 ml of acetone. Solution occured gradually over a 15 hr period. Removing volatiles left the crude solid product, which was crystallized from 30 ml of water to yield 3.5 g (83%) of crystalline 3-homopiperonylmeconin-3-carboxamide (21), mp 177-178° (prelim. softening). Another crystallization from benzene brought the melting point to 177.7-178.7°.

Anal. Calcd. for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97. Found: C, 62.2; H, 5.0.

Attempts at Isomerizing 3-Homopiperonylmeconin-3-carboxamide (21) to 4-Hydroxy-4-homopiperonyl-7,8-dimethoxyhomophthalimide (23). - Heating the dry carboxamide at 185-190° for 2.5 hr effected no change. Liquid ammonia with some methanol at room temperature for 1 day gave only unchanged starting material, as did alcoholic-concentrated aqueous ammonia at 100°, or sodamide in liquid ammonia at -43°.

While concentrated aqueous ammonia at 100° gave no reaction, raising the temperature to 150-180° produced a new compound, which on recrystallization

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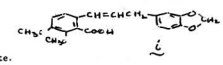
from 95% ethanol melted at 90-91°. This material, considered to be a disubstituted propene i, was soluble in aqueous alkali, and decolorized dilute



i

permanganate.

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 66.66; H, 5.30; O, 28.04. Found: C, 66.5; H, 5.77; O, 27.81.

In the light of a successful analogous conversion of 3-phenylphthalide-3-carboxamide to 4-hydro-4-phenylhomophthalimide,[12] this reluctance of 21 to isomerize is not clear. Possibly the methoxy group at the 6-position of meconin 21 tends to stabilize the lactone ring.[25]

3-Homopiperonylmeconin-3-carboxylic Acid (22) from the Amide 21. - A solution of the amide 21 (1.4 g) in 55 ml of 20% aqueous sodium hydroxide plus 17 ml of alcohol was refluxed for 3 hr. The reaction mixture was concentrated to about half its volume, diluted with an equal volume of water, and acidified with 20% sulfuric acid. The product was taken up in chloroform, and the extract was dried and then stripped of all solvent. Crystallization of the residue from benzene furnished 1.1 g (83%) of the desired 3-homopiperonylmeconin-3-carboxylic acid (22), mp 142.5-143.5°; ir (KBr) 3260, 2790, 1745, 1688 cm^{-1}. A sample further recrystallized for analysis showed mp 145.5-147°.

Anal. Calcd for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70. Found: C, 62.2; H, 4.8.

Attempts at obtaining this acid by treating the amide 21 with nitrous acid failed, as did attempts at hydrolyzing the precursor 3-cyano-3-homopiperonylmeconin (20) with acid. Thus 36% hydrochloric acid at 150° for 1 hr resulted in charring, while 24% hydrochloric acid at 130° for 1 hr gave only unchanged cyano compound. This resistance to acid hydrolysis, contrasting sharply with the facile hydrolysis of 3-cyano-3-methylmeconin (16), may be attributed to steric factors.

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3-Homopiperonylmeconin-3-carboxylic acid (33=22) was also obtained by an oxidative process from α-(homopiperonyl)-2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (29) as described below.

2-Carboxy-3,4-dimethoxyphenylacetonitrile (27). - A solution of the 2-nitroso derivative[14] (22 g) of 6,7-dimethoxyindanone (26) in 200 ml of 8% aqueous sodium hydroxide was stirred and treated dropwise with 22 g of p-toluenesulfonyl chloride. The mixture was then warmed to 80° before chilling in an icebath and acidifying with 10% hydrochloric acid. The solids deposited overnight at icebox temperatures were collected, washed with water, and dried. Crystallization from benzene afforded 2-carboxy-3,4-dimethoxyphenylacetonitrile (27), mp 97-99° [lit.[14] mp 104-108°] in yields up to 72%. The same product 27 was obtained with phosphorus pentachloride,[14] but the yields were low.

2-Carbomethoxy-3,4-dimethoxyphenylacetonitrile (28). - 2-Carboxy-3,4-dimethoxyphenylacetonitrile (27) (7.5 g; 79 mmol) suspended in 20 ml of ether was treated with ethereal diazomethane in excess first in the icebath and then at room temperature. Crystallization of the crude product from ethanol-water gave pale yellow needles (5.4 g; 83%) of 2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (28), mp 44.5-45°. A sample for analysis was prepared by distillation at bp 153° (0.7 mm).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.3; H, 5.7; N, 6.0.

α-(Homopiperonyl)-2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (29). - 2-Carbomethoxy-3,4-dimethoxyphenylacetonitrile (28; 10 g; 42 mmol) was added to benzene (150 ml freshly distilled from calcium hydride) containing comercial sodamide (1.67 g; 42 mmol), and the mixture was stirred and refluxed for 1hr. The glassware had been rigorously dried, and a slow stream of nitrogen was maintained through the apparatus during the course of the reaction. Homopiperonyl iodide was then added (8.8 g; 32 mmol), and the refluxing was continued for 1 day.

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Acetic acid (3.3 ml) in 100 ml of water was introduced, and the aqueous layer was extracted with benzene and with ether. The combined organic layers were rinsed with water, dried, and stripped of solvent. Fractionation of the oily residue (17.4 g) in a short-path, 3-bulb still gave a lower boiling mixture of starting materials (5.2 g), distilling at bath temperatures up to 185° (0.02 mm) and a higher boiling fraction (7.9 g), bp 180-240° (0.02 mm), containing the product. Two crystallizations of this material from acetic acid-water furnished α-(homopiperonyl-2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (29), mp 60.5-62.0°, in yields of 26-36%; ir max 2240, 1731 cm^{-1}. Further recrystallization gave constant-melting material, mp 63.5-65.0°.

Anal. Calcd. for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52; N, 3.65; methoxy, 24.3. Found: C, 65.7; H, 5.4; N, 3.7, methoxy 24.1.

When the same alkylation was carried out at room temperature with the reactants in absolute methanol containing dissolved sodium, the initial alkalinity gradually decreased until after 16 hr, 85% had been lost. Two products could be isolated from this reaction: (a) 7,8-dimethoxyhomophthalimide, with the same melting point (209-210°) and infrared absorption curve as the identical material (mp 208-209.5°) obtained by baking 3,4-dimethoxyhomophthalic acid[14] with ammonium carbonate [Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 60.0; H, 4.8; N, 6.4.] and (b) a water-white liquid bp 40-45° (0.7 mm); n_D^{25} 1.5763; ir absorption max 3080, 2980, 1630, 988, 904 cm^{-1}, which decolorized bromine in carbon tetrachloride instantly and which was taken as 3,4-methylenedioxystyrene [Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.8; H, 5.4].

4-Hydroxy-4-homopiperonyl-7,8-dimethoxyhomophthalimide (32) from Cyano-ester 29. - A solution of the cyano-ester 29 in acetone (35 ml) was treated with 15 ml of water containing 9 ml of 28% hydrogen peroxide followed by 2.1 ml of 8% aqueous sodium hydroxide, and the mixture was allowed to stand for 2 days.

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After volatiles were removed from the warm solution in a jet of air, the residue was taken up in ether, and the ether solution washed with water, dried, and stripped of solvent. The remaining solids, recrystallized from aqueous acetic acid, afforded 4-hydroxy-4-homopiperonyl-7,8-dimethoxyhomophthalimide, mp 118-119°, in low yield; ir max 3360, 3200, 1714, 1690 cm^{-1}; soluble in cold 8% aqueous sodium hydroxide.

Anal. Calcd. for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.64. Found: C, 62.2; H, 5.3; N, 3.6.

3-Homopiperonylmeconin-3-carboxylic Acid (33) from Cyano-ester 29. - A solution of cyano-ester 29 (3.0 g), 100 ml of acetone, 45 ml of water, 27 ml of 28% aqueous hydrogen peroxide, and 6.3 ml of 8% sodium hydroxide was kept at 15° for 1 hr, then at room temperature for 3 days, and thereafter treated essentially as in the isolation of crude 4-hydroxy-4-homopiperonyl-7,8-dimethoxyhomophthalimide (32).

A portion of this light-yellow oily material 32 (1.5 g) was refluxed with ethanol (17 ml) and 20% aqueous sodium hydroxide (60 ml) for 1 day in an atmosphere of nitrogen. After concentrating the mixture at steam-temperatures at reduced pressures, it was diluted with water, acidified with hydrochloric acid, and extracted with chloroform. The chloroform solution was dried, stripped of solvent, and the residue crystallized from aqueous acetic acid to give 3-homopiperonylmeconin-3-carboxylic acid (33), mp 142-143.5° in 38% yield; bicarbonate soluble; ir (KBr) 3280, 2860, 1740, 1690 cm^{-1}. Further recrystallization from aqueous acetic acid furnished colorless plates of 33, mp 143-144°.

Anal. Calcd. for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70; neturalization eqv., 386.3. Found: C, 62.14; H, 4.56; N, 0.0; neturalization eq., 399.5.

The nonidentity of this product with the α-homopiperonyl-2-caroxy-3,4-dimethoxyphenylacetic acid described in the literature[15] was established by directly comparison with an authentic sample made available by Professor A.S.

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Bailey. The melting points, taken on a Fisher-Johns apparatus, were found to be 147-148° for compound 33, 152-153° for Bailey's homophthalic acid (cf. 31), and 123-128° (previous softening) for the mixture. The infrared absorption curves of the two materials showed many points of difference.

The identity of the product 33 described here with the 3-homopiperonylmeconin-3-carboxylic acid (22) obtained as described before from 3-homopiperonyl-3-carboxamide (21) was supported by melting point comparison (Fisher-Johns: 147-148° vs. 145.5-147°), by the virtual identity of the two infrared absorption spectra, and by decarboxylation of the present product to 3-homopiperonylmeconin (34).

3-Homopiperonylmeconin (34) from 3-Homopiperonylmeconin-3-carboxylic Acid (33). - A sample of the acid 33 was distilled in a wide-bore short-path still at outside temperatures of 240-300° (0.4 mm). Two crystallizations of the distillate from ethanol gave white, fluffy crystals of 3-homopiperonylmeconin (34), mp 81.5-82°; ir max 1748 cm^{-1}. The lactone carbonyl peak compares well with that observed for 3-methylmeconin (18) and for 3-homopiperonylmeconin-3-carboxylic acid (22).

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.5; H, 5.3.

4-Homopiperonyl-7,8-dimethoxyhomophthalimide (25). - No change noted when α-(homopiperonyl)-2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (29) was heated at 200-320° for 0.5 hr or was exposed to the action of ethereal hydrogen chloride in the absence or presence of anhydrous zinc chloride.

1. Acid hydrolysis of cyano-ester 29 followed by cyclization with alkali. - Dry hydrogen chloride was bubbled for 5 hr into an ice-cold solution of 0.1 g of α-(homopiperonyl)-2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (29) in 12 ml of acetic acid. The mixture was allowed to stand in the cold for 2 days. Stripping off all volatile material left a residue, which was dissolved in ether and washed with water. Removing the solvent furnished a partially puri-

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fied product, insoluble in warm 5% bicarbonate [ir max 3442, 3335, 1718, 1689, but not at 2240 cm^{-1} (nitrile)] and considered to be α-(homopiperonyl)-2-carbomethoxy-3,4-dimethoxyphenylacetamide (30). Solution occurred when this ester-amide was treated with 2 ml of oxygen-free 8% aqueous sodium hydroxide with intermittent warming on the steam for 15 min. Acidification of the cooled solution with dilute hydrochloric acid deposited a gum, which was collected, and rubbed with a small volume of cold ethanol. The resulting white crystals (0.05 g) of 4-homopiperonyl-7,8-dimethoxyhomophthalimide (25), mp 124.5-125°, showed an infrared absorption spectrum identical to that of the same compound described below. The mixture melting point was 125-126°.

2. Saponification of 29 followed by cyclization. - A mixture of 3.5 g (9.2 mmol) of cyano-ester 29 with 100 ml of 8% sodium hydroxide and 70 ml of ethanol was refluxed for 2 hr. The resulting solution, concentrated under reduced pressures to about $^1/_3$ its volume, was diluted with 100 ml of water and acidified with hydrochloric acid. After cooling the mixture overnight, it was filtered, and the solids (presumably homophthalic acid 31) were dissolved in concentrated aqueous ammonia. The solution was evaporated to dryness at 100° (reduced pressures), and the foamy residue was powdered and then thoroughly mixed with ammonia carbonate (1.1 g). The solids were heated for 50 min in an oilbath at 165° (reduced pressures). The reaction mixture was dissolved in ca. 75 ml of ethanol, and the solution was concentrated in the presence of decolorizing charcoal to ca. 30 ml, filtered, and finally cooled overnight. The precipitate was collected and crystallizedtwice from ethanol to get 4-homopiperonyl-7,8-dimethoxyhomophthalimide (25) as fine white needles, mp 126-127°, in 61% yield; ir (mineral mull) 3155, 3079, 1700, 1670 cm^{-1}; insoluble in hot 5% aqueous sodium bicarbonate, but soluble in cold dilute sodium hydroxide to give a deep yellow solution.

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Anal. Calcd. for $C_{22}H_{21}NO_6$: C, 65.03; H, 5.19; N, 3.79; methoxy, 16.8. Found: C, 65.1; H, 5.3; N, 3.8; methoxy 16.7.

With determinations made using a Fisher-Johns apparatus instead of a melting-point bath, a sample of homophthalimide 25 prepared and provided by Bailey[15] showed mp 130-131.5°, and the product described above showed mp 128.5-130°; a mixture of the two showed mp 128.5-130°. The infrared absorption spectra of both samples taken as pellets in KBr were identical and included peaks at 3310 and 1672 cm^{-1}.

4-Hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium Hydrochloride (42).[5] - A stoppered mixture of 2,3-dimethoxybenzylaminoacetal (1) (2.8 g; 0.010 mol) and 50 ml of 6 N hydrochloric acid was allowed to stand overnight at room temperature. Evaporation of the mixture under reduced pressure (100°) left a red oil, which was crystallized once from 1:1 ether-ethanol and three time from methanol. The desired product 42 as the hydrochloride[26] (1.7 g or 68%) was obtained with mp 170-171°; uv max (7 x 10^{-5} M in absolute ethanol) 229 nm (log ε 3.9), 278 (3.2);[27] ir (mineral oil mull) 3475, 1640, 1605, 1580 cm^{-1}.

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: C, 53.77; H, 6.56; N, 5.70. Found: C, 53.68; H, 6.40; N, 5.70.

That the corresponding 4-ethoxy compound 43 was also present was shown by mixing the crude red oil with acetone, whereupon a pale yellow solid precipitated. Two crystallizations of this solid from ethanol gave crystals (20% yield) of 4-ethoxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium chloride (43), mp 147-148° (preliminary coloration); ir (mineral oil mull) almost superposable with the curve from the 4-hydroxy compound 42; nmr (D_2O) δ 7.22 (q, J=8.5,2.5, 8.5, 2, H-5 and 6), 4.45 and 4.41 (s's, 2, 2H-1), 3.94 and 3.86 (s's, 7,8-diCH$_3$O), 3.67 (m, CH$_3$-O-CH-CH$_3$), 1.27 ppm (t, J=7, 3, CH$_3$CH$_2$-). Integration between δ 3.94 and 3.67 ppm showed 11 protons as required.

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The methiodide was prepared by treating the hydrochloride of 43 with dilute aqueous sodium carbonate, extracting the basic mixture with chloroform, and removing solvent from the dried chloroform solution. Distillation of the residual oil furnished the base, bp 141° (0.05 mm), corresponding to the 4-ethoxy compound 43. The distilled material was stirred with methyl iodide (3 molar equivalents) in benzene under nitrogen for 1 hr. The solids were collected and washed with dry benzene to give analytically pure 2,2-dimethyl-4-ethoxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium iodide, mp 220-222°.

Anal. Calcd. for $C_{14}H_{22}INO_3$: C, 45.80; H, 6.15; N, 3.56. Found: C, 46.03; H, 6.22; N, 3.68.

Although we believe the 4-ethoxy compound 43 was present in the crude product, its formation from the 4-hydroxy compound during the crystallizations from ethanol has not been precluded.[28]

2-Methyl-4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (36). - The yellow solution obtained on mixing o-veratraldehyde (8.3 g; 0.050 mol) with aminoacetal (6.7 g; 0.050 mol) in 75 ml of absolute ethanol was hydrogenated over platinum to form 2,3-dimethoxybenzylaminoacetal (1).[5] Formaldehyde (4.5 g of 37% formalin, or 0.056 mol) plus 5 ml of acetic acid were added and the hydrogenation was continued until another 0.05 mol of hydrogen was taken up.[1] Removal of the catalyst and all volatiles left 14 g (97%) of colorless oily N-methyl-N-(2,3-dimethoxybenzyl)-aminoacetal (25).

Cyclization was effected by allowing a solution of this acetal (5.7 g or 0.020 mol) in 100 ml of 6N hydrochloric acid to stand at room temperature for one day. Bringing the reaction mixture to pH 10 by adding 6N sodium hydroxide at temperatures no higher than 10° precipitated almost pure 2-methyl-4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (36) in ca. 90% yield. Extracting the filtrate with ether afforded more of the same product, which when combined with the original crop melted at 135-136° either before or after

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crystallization from 1:1 ether-alcohol. This material should not be warmed unnecessarily. The free base 36 showed uv max (1 x 10^{-4} M in C_2H_5OH) 229 nm (sh)(log ε 3.67), 278 (2.93);[25] nmr ($CDCl_3$) δ 6.87 (q, J=8,10.8 Hz, 2, H-5,6), 4.45 (m, 1, HCOH), 3.75 and 3.73 (s's, 6, 7,8-diCH$_3$O), 3.71, 3.08 (d, J=16 Hz, as AB, 2, 2H-1), 2.56 (m, 2, 2-H-3), 2.33 ppm (s, 3, N-CH$_3$).

The hydrochloride of 36 was prepared by bubbling dry hydrogen chloride into an ether solution of the base. Two crystallizations of the precipitate from ethanol gave yellow, analytically pure hydrochloride, mp 183-184°; uv max (7 x 10^{-5} M in C_2H_5OH) 229 nm (log ε 4.1), 279 (3.3); ir ($CHCl_3$) 3325, 2575, 1605 cm^{-1}; nmr (D_2O) δ 7.96 (q, J=7,3.7, 2, H-5 and 6), 4.96 (t, J=2, 1, HCOH), 4.38 (q, J=16,8,16, 2 2H-1), 3.77 and 3.73 (s's, 6, 7,8-diCH$_3$O), 3.53 (m, 2, 2H-3), 3.10 ppm (s, 3, $CH_3\overset{+}{N}$).

Anal. Calcd. for $C_{12}H_{18}ClNO_3$: C, 55.49; H, 6.98; N, 5.39;. Found: C, 55.45; H, 6.94; N, 5.44.

2-Methyl-4-oxo-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (37). - 4-Hydroxy compound 36 (2.2 g; 10 mmol) was added in portions to a stirred solution of 0.65 g (6.5 mmol) of chromium trioxide in 50 ml of water plus 15 ml of concentrated sulfuric acid. The reaction mixture protected with a blanket of nitrogen, and was held at temperatures below 10°. After stirring at 0-10° for 1 hr, the solution was stored overnight at room temperature. The cold solution was then rinsed with ether (discard), and with cooling was brought to pH 10. Without delay the basic mixture was extracted thoroughly with chloroform, and the dried extracts were stripped of all solvent (temperature below 40°). Crystallization of the residual yellow oil from chloroform yielded 1.3 g (55%) of 2-methyl-4-oxo-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (37), mp 93-97°; uv max (3 x 10^{-5} in C_2H_5OH) 229 nm (log ε 4.22), 279 (4.04); ir ($CHCl_3$) 1685 cm^{-1}; nmr ($CDCl_3$) δ 7.78 (d, $J_{5,6}$=8.5, 1, H-5), 6.87 (d, $J_{5,6}$=8.5, 1, H-6), 3.93 and 3.83 (s's, 7,8-diCH$_3$O), 3.75 (s, 2H-1), 3.24 (s, 2, 2H-3), 2.51 ppm (s, 3, CH$_3$-N). The integration between δ 3.93-3.75 ppm corresponded to 8 protons.

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The picrate of 37, recrystallized from methanol, showed mp 178-180°.

Anal. Calcd. for $C_{18}H_{18}N_4O_{10}$: C, 48.01; H, 4.03; N, 12.44. Found: C, 48.17; H, 3.84; N, 12.67.

Since the free base 37 was very susceptible to air oxidation, it was advantageous to store the material as its hydrochloride, which was precipitated by bubbling dry hydrogen chloride into a solution of the base in anhydrous ether. Crystallization without delay from 95% alcohol gave pale yellow crystals of 2-methyl-4-oxo-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium chloride, mp 192-195° (decomp); ir (mineral oil mull) 1680 cm^{-1}; nmr (D_2O) δ 7.85 (d, J=8, 1, H-5), 7.20 (d, J=8, 1, H-6), 4.70 (s, 2, 2H-3), 4.20 (s, 2, 2H-1), 3.93 and 3.73 (s's, 6, 7,8-diCH$_3$O), 3.17 ppm (s, 3, $CH_3\overset{+}{N}$).

The N-benzyl derivative corresponding to the N-methyl compound 37 has been reported[29] with absorption constants that compare well with those given above.

2-Methyl-4-hydroxy-4-homopiperonyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (38) by Grignard Addition of Homopiperonylmagnesium Bromide to 4-Keto Compound 37. - A mixture of homopiperonyl bromide (2.8 g; 12 mmol), 0.3 g (12 mmol) of resublimed magnesium, and 35 ml of tetrahydrofuran freshly distilled from lithium aluminum hydride was refluxed for 0.5 hr until the magnesium had disappeared. The reaction was carried out under dry nitrogen in scrupulously dried glassware. 2-Methyl-4-oxo-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium chloride 37 (1.7 g; 5.5 mmol) that had been carefully dried in vacuo was added in portions to the cold Grignard solution from a flask connected to the reaction vessel by a wide rubber hose. After 1 hr of reflux, the mixture was quenched over ice. Product was extracted into chloroform, and the chloroform solution was washed once with water, dried with magnesium sulfate, and stripped of all volatiles at room temperature under reduced pressure. Rubbing the residual yellow oil with a little methanol produced 1.4 g (69%) of almost pure addition product 38 as tan crystals, mp 112-115°. Recrystallization from methanol gave material, mp 118-118.5° which was homogeneous according to thin-layer chromatography (methanol-chloroform, 4:1); uv max (95% C_2H_5OH) 206 nm (log ε 4.57), 228 sh (4.05), 281 (3.61); ir (mineral oil mull) 3420, 1600 cm^{-1}; nmr ($CDCl_3$) δ 6.98 (d, J=8, 1, H-6), 6.55 (d, J=8, 1, H-5), 6.40 (s, 3, piperonyl Ar H's), 5.63 (s, 2, $CH_2(O)_2$), 3.65 (s, 6, 7,8-diCH$_3$O), 3.52 and 3.28 (d's, 2, 2H-1), 2.8-2.0 (m, CH$_3$-C-CH$_2$CH$_2$), 2.23 ppm (s, CH$_3$-N). Integration from δ 2.0-2.8 ppm indicated 9 protons.

Anal. Calcd. for $C_{21}H_{25}NO_6$: C, 67.91; H, 6.94; N, 3.76. Found: C, 68.20; H, 6.99; N, 3.64.

When exposed to air for extended periods, the Grignard adduct 38 showed signs of change. The hydrochloride of 38 precipitated from aqueous-alcoholic hydrochloric acid and, when recrystallized from alcohol, was obtained as white crystals, mp 142-145°; uv max (2 x 10^{-5} M in C_2H_5OH) 229 nm (log ε 4.34), 281 (4.11).

Preliminary trials indicated that the Grignard addition using phenethylmagnesium bromide instead of homopiperonylmagnesium bromide would offer no complications.

4-Hydroxy compound 38 warmed in methanol containing various concentrations of hydrochloric acid gave mixtures. Exposure to hydrochloric acid in acetic acid converted the 4-hydroxy compound to the disproportionation products, the tetrahydro and the fully aromatic isoquinolines, 41 and 39, respectively.

2-Methyl-4-homopiperonyl-7,8-dimethoxyquinolinium Iodide (39). - A solution of the 4-hydroxy-4-homopiperonylisoquinoline 38 (0.50 g; 1.4 mmol) in 30 ml of methanol was added to a mixture of potassium acetate (2.5 g; 24 mmol) and 1.3 g (10 mmol) of iodine with 30 ml of 95% alcohol. After a 0.5 hr reflux

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period, the mixture was cooled, and the green precipitate was collected, dissolved in boiling methanol (20 ml), and treated with a few crystals of sodium sulfite until the color became yellow. Filtering the hot solution removed unwanted solids, and cooling the filtrate deposited yellow needles (0.55 g; 85%) of 2-methyl-4-homopiperonyl-7,8-dimethoxyisoquinolinium iodide (39), mp 176-178°. A sample recrystallized from CH$_3$OH melted at 180-181°; uv max (95% C_2H_5OH) 217 nm (log ε 4.56), 254 (4.61), 287 (3.89);[27] ir (mull) 1600, 1275 cm^{-1}; nmr (F_3CCOOH, external TMS) δ 9.00 (s, 1, H-1) 7.60 (s, 2, H-5,6), 7.40 (br s, 1, H-3), 6.20 (br s, 3 piperonyl Ar H's), 5.46 (s, 2, $CH_2(O)_2$), 4.03 (s, 3, $CH_3\overset{+}{N}$), 3.85 and 3.72 (s's, 6, 7,8-diCH$_3$O), 3.2-2.6 ppm (m, 4, CH_2CH_2).

2-Methyl-4-homopiperonyl-7,8-dimethoxy-1,2-dihydroisoquinoline (40). - 2-Methyl-4-homopiperonyl-7,8-dimethoxyisoquinolinium iodide (0.50 g; 1.0 mmol) was added in portions to a suspension of lithium aluminum hydride (0.8 g; 20 mmol) in 50 ml of dry ether.[19] The mixture under nitrogen was stirred for 4 hr at room temperature. Just enough aqueous 33% sodium potassium tartrate was added to coagulate the white precipitate. The supernatant ether was separated by decanting, solvent was removed in a stream of nitrogen at 35°, and the pink residue was crystallized quickly from 95% ethanol to give faintly pink needles (0.33 g; 93%) of 2-methyl-4-homoperonyl-7,8-dimethoxy-1,2-dihydro-

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isoquinoline (40), mp 60-64°. Further crystallization (nitrogen) raised the melting point to 64-65°.

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 71.36; H, 6.56; N, 4.04. Found: C, 71.86; H, 6.32; N, 3.99.

Catalytic microhydrogenation showed that the dihydroisoquinoline 40 absorbed 0.90 mole of hydrogen as compared with the required 1.0 mole; ir (mineral oil mull) 1630 cm^{-1}; nmr ($CDCl_3$) δ 6.57 (s, 2, H-5,6), 6.50 (broad s, 3, piperonyl Ar H's), 5.70 (s, 2, $CH_2(O)_2$), 5.60 (broad s, 1, H-3), 3.98 (s, 2, 2H-1), 3.67 (s, 6, 7,8-diCH$_3$O), 3.0-2.15 (m, CH_2CH_2), 2.55 ppm (s, CH$_3$-N). The signals at δ 3.0-2.15 ppm corresponded to 7 protons.

Exposure of the dihydroisoquinoline 40 under a nitrogen atmosphere to hot methanolic hydrochloric acid led to disproportionation, with formation of tetrahydroisoquinoline 41 and the full aromatic isoquinoline 39 in approximate yields of 45-50% and 40% respectively. Exposure to acid at concentrations of dihydroisoquinoline as low as 0.5 g in 5 liters gave essentially the same results.

2-Methyl-4-homopiperonyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (41) by Borohydride Reduction of Isoquinoline Methiodide 39. - Excess sodium borohydride (0.9 g) was added in portions to a stirred solution of 2-methyl-4-homopiperonyl-7,8-dimethoxyisoquinolinium methiodide (39) (0.90 g; 1.8 mmol)

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in 100 ml of ethanol plus 100 ml of water. After warming on the steambath for 1 hr, solvent was removed under reduced pressure at 100°, and the residual gum was dissolved in ether. Introducing dry hydrogen chloride precipitated an oil, which was collected, suspended in water, and treated with 10% aqueous sodium hydroxide. Product was extracted from the alkaline mixture with chloroform, and the dried extract, concentrated to ca. 2 ml, was chromatographed through acid-washed alumina. The eluting solvents were benzene (125 ml) followed by 1:1 benzene-chloroform. The pale yellow oil (0.19 g; 30%) that emerged with the benzene-chloroform was taken as the desired tetrahydroisoquinoline 41; nmr ($CDCl_3$) δ 6.70 (d, J=5, 2, H-5,6), 6.58 (s, 3, piperonyl Ar H's), 5.76 (s, 2, $CH_2(O)_2$), 3.74 (s, 6, 7,8-diCH$_3$O), 3.9-3.3 (m, 2, 2H-1), 2.9-1.75 (m, $CH_2CH_2CHCH_2$), 2.4 ppm (s, CH$_3$-N). The 2.9-1.75 signals integrated to 10 protons.

The methiodide was prepared for characterization by allowing the tetrahydroisoquinoline 41 to stand for 3 days in a solution of methyl iodide (2 ml) in methanol (0.5 ml). Evaporation of volatile material from the reaction mixture followed by crystallization from alcohol gave white crystalline 2,2-dimethyl-4-homopiperonyl-7,8-dimethoxy-tetrahydroisoquinolinium iodide, mp 132-134°.

Anal. Calcd. for $C_{22}H_{28}INO_4$: N, 2.81. Found: N, 2.91.

dehydrogenation with iodine afforded the corresponding 4-substituted isoquinoline **39** in a minimum overall yield of 28% in the five steps from acetal **1**. The Py-reduced isoquinolines **40** and **41** were derived from **39** by treatment, respectively, with lithium aluminum hydride in ether[2,19] and with sodium borohydride in ethanol. When aminoacetal **1** was cyclized without N-methylation, the 4-hydroxytetrahydroisoquinoline **42**[5] was obtained, evidently mixed with the 4-ethoxy compound **43**. Oxidation of the hydroxy compound **42** to the 4-keto derivative was realized, but purification presented problems.

4-Ketotetrahydroisoquinolines analogous to **37** are

known[1] but, so far as we could find, they have not been prepared from 4-hydroxytetrahydroisoquinolines. Although related Grignard additions are also known,[20] they have been limited in number, probably because the 4-keto compounds have been hard to make.

In summary, we have described examples of several generally applicable syntheses of 4-substituted isoquinolines.

Acknowledgment. We wish to acknowledge the support of the American Cancer Society through Research Grant T-300 and through an allotment from a Rebecca Rice Institutional Grant (37D). We are indebted to the U.S. Public Health Service for a Research Fellowship to one of us (A.L.B.). We thank Professor A. S. Bailey for his kindness in supplying samples of α-(2-carboxy-3,4-dimethoxyphenyl)-α-homopiperonylacetic acid (**24** = **31**) and 4-homopiperonyl-7,8-dimethoxyhomophthalimide (**25**), and Drs. A. H. Homeyer and A. E. Ruehle (Mallinckrodt Chemical Works) and L. G. Mumm (New York Quinine and Chemical Works) for generous quantities of narcotine. Professor F. Santavý very kindly sent us some pertinent ultraviolet absorption data, and Professor James M. Bobbitt provided several stimulating discussions.

Registry No.—**1**, 53762-16-6; **2** HCl, 55762-17-7; **3**, 53762-18-8; **3** HCl, 53762-19-9; **3** picrate, 53762-20-2; **3** quaternary chloride, 53762-66-6; **4**, 53762-21-3; **4** HCl, 53762-22-4; **4** picrate, 53798-66-6; **5** picrate, 53762-24-5; **6** picrate, 53762-26-8; **7**, 53762-27-9; **7** picrate, 53762-28-0; **8**, 53762-29-1; **8** HCl, 53762-30-4; **9** HCl, 53762-31-5; **10**, 53762-32-6; **11**, 53762-33-7; **12**, 53762-34-8; **13**, 53762-35-9; **14**, 519-05-1; **15**, 53783-46-3; **16**, 53762-36-0; **17**, 53762-37-1; **18**, 53762-38-2; **19**, 53762-39-3; **20**, 53762-40-6; **21**, 53762-41-7; **22**, 53762-42-8; **25**, 53762-43-9; **26**, 53762-44-0; **27**, 53762-45-1; **28**, 53762-46-2; **29**, 53762-47-3; **30**, 53762-48-4; **32**, 53762-49-5; **34**, 53762-50-8; **35**, 53762-51-9; **36**, 53366-13-5; **36** HCl, 53762-52-0; **37**, 53762-53-1; **37** picrate, 53762-54-2; **37** HCl, 53762-55-3; **38**, 53762-56-4; **38** HCl, 53762-57-5; **39**, 53762-58-6; **40**, 53762-59-7; **41**, 53762-60-0; **41** methiodide, 53762-61-1; **42** HCl, 53762-62-2; **43**, 53762-63-3; **43** HCl, 53762-64-4; **43** methiodide, 53762-65-5; i, 53762-67-7; glyoxylic acid, 298-12-4; veratryl chloride, 7306-46-9; benzyl chloride, 100-44-7; piperonyl chloride, 20850-43-5; piperonyl alcohol, 495-76-1; thionyl chloride, 7719-09-7; 6-nitropiperonyl chloride, 15862-98-3; narcotine, 128-62-1; homopiperonyl bromide, 23808-46-0; phosphorus tribromide, 7789-60-8; homopiperonyl alcohol, 6006-82-2; *N*-homopiperonylpyridinium bromide, 53762-68-8; homopiperonyl iodide, 53762-69-9; *N*-homopiperonylpyridinium iodide, 53762-70-2; 7,8-dimethoxyhomophthalimide, 53762-71-3; 3,4-dimethoxyhomophthalic acid, 3723-02-2; 3,4-methylenedioxystyrene, 7315-32-4.

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(27) Professor F. Šantavý has determined related ultraviolet absorption maxima: (a) for the free base **42**,[5] uv max (ethanol) 226 nm (sh) (log ε 3.95), 274 (3.2), 278 (3.19); (b) for 2-methyl-7,8-dimethoxyisoquinolinium iodide,[5] uv max (ethanol) 219 nm (log ε 4.4), 258 (4.4), 296 sh (3.6), 3.96 (3.6).
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Synthesis of Ring-Fused Pyrroles. II. 1,3-Dipolar Cycloaddition Reactions of Munchnone Derivatives Obtained from Tetrahydroisoquinoline-1-carboxylic Acids

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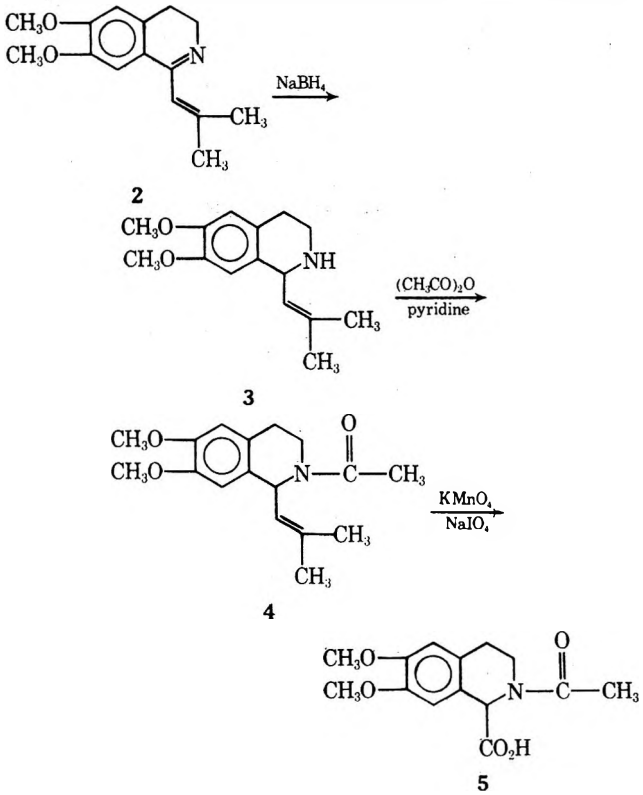
Received June 20, 1974

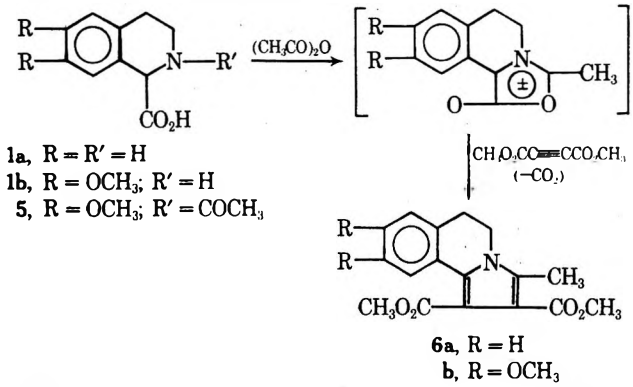
The reactions of mesoionic oxazolium 5-oxides (munchnones) derived from 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**1a**, **1b**, and **5**) are reported and involve the 1,3-dipolar cycloaddition to the acetylenic dipolarophiles, dimethyl acetylenedicarboxylate and phenylacetylene. In the latter case, the reaction was found to be regiospecific, yielding **7a** and **7b**, respectively, as the only products. An isomeric pyrrolo[2,1-*a*]isoquinoline (**8**) was prepared by an unambiguous route and a comparison of the PMR spectra of **7a** and **8** is presented. Furthermore, irradiation of a methanolic solution of **7a** in the presence of trace amounts of iodine resulted in a photocylization yielding the indolizinophenanthrene (**9a**). Unsuccessful attempts at the preparation of the analog, **9b**, *via* photocyclization or Pschorr cyclization reactions are also discussed.

The conversion of secondary amino acids into pyrroles via intermediate mesoionic oxazolium 5-oxides (munchnones)[1] has been utilized in converting the "cyclic" amino acids, tetrahydro-β-carboline-1- and -3-carboxylic acids, into novel indolizinoindoles.[2] This paper will report on the above reaction with another type of cyclic amino acid ring system, namely, the 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids, and the subsequent synthetic use of a pyrrolo[2,1-*a*]isoquinoline in a photocyclization reaction will be discussed.

For the purposes of this study, 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, **1a**, was prepared by the catalytic hydrogenation of isoquinoline-1-carboxylic acid,[3] which in turn was synthesized from isoquinoline via a Reissert reaction[4] and subsequent acid hydrolysis of the Reissert salt.[5] The preparation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1b**), however, was not as straightforward. Reaction of homoveratrylamine with glyoxylic acid furnished **1b** in low and variable yields (0–20%).[6] An alternate, though circuitous, synthesis was used here and involved the sodium borohydride reduction of **2**[7] and subsequent acetylation of the tetrahydroisoquinoline **3** with acetic anhydride–pyridine to furnish the amide **4**. Oxidative cleavage of the olefinic substituent of **4** using either ozone, followed by a hydrogen peroxide work-up, or reaction with ruthenium tetroxide failed to give the desired *N*-acetyl tetrahydroisoquinoline-1-carboxylic acid, **5**. This oxidative cleavage reaction was successfully carried out, however, when potassium permanganate–sodium metaperiodate was used.[8]



Since the first step in the formation of the oxazolium 5-oxide involves N-acetylation of the amino acid, compound **5** would represent a suitable reactant for this reaction, since it would be formed in situ from **1b** and acetic anhydride. In fact, when either **1b** or **5** was treated with dimethyl acetylenedicarboxylate and acetic anhydride, the corresponding pyrrolo[2,1-*a*]isoquinoline, **6b**, was isolated in 65–80% yields. In a similar manner, the tetrahydroisoquinoline **1a** provided **6a** in 62% yield.



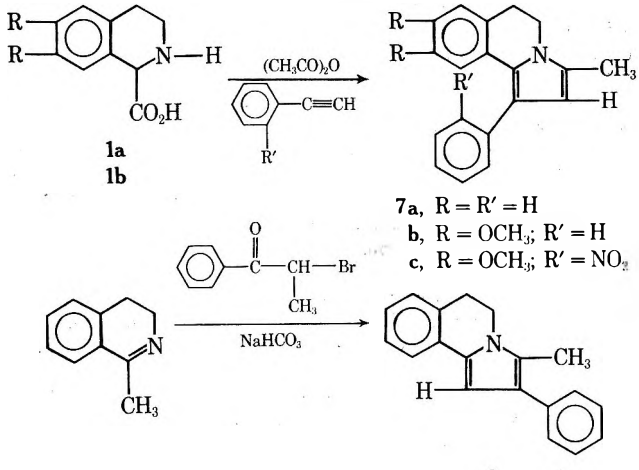
1a, R = R′ = H
1b, R = OCH_3; R′ = H
5, R = OCH_3; R′ = $COCH_3$

6a, R = H
b, R = OCH_3

The use of phenylacetylene as the dipolarophile in this particular 1,3-dipolar cycloaddition reaction has been reported previously and has been observed to be regiospecific in its reaction with the munchnone dipoles used thus far.[1,2] When phenylacetylene was allowed to react with either **1a** or **1b** in acetic anhydride, once again a single product, **7a** and **7b**, respectively, was isolated in good yield. The structure assignments for these products were made in the following manner: 2-phenyl-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (**8**) was prepared by treating 1-methyl-3,4-dihydroisoquinoline with α-bromopropiophenone under mild alkaline conditions using the procedure of Casagrande.[9] A comparison of the two isomeric pyrrolo[2,1-*a*]-isoquinolines, **7a** and **8**, was made by ^1H NMR spectroscopy and the expected differences in the chemical shifts and coupling constants for the pyrrole ring protons for each compound were noted.

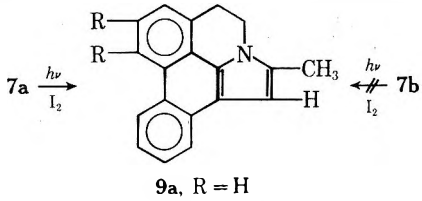
While the pyrrole ring proton (H-2) for compound **7a** appeared at δ 6.00 as a quartet with long-range coupling to the adjacent methyl group (J_{H,CH_3} = 1.0 Hz),[1] the pyrrole ring proton of 8 (H-1) was observed at δ 6.68 as a sharp singlet. The deshielding of H-1 in 8 vs. H-2 in **7a** is undoubtedly due to the anisotropic effect of the aromatic carbocyclic portion of the tetrahydroisoquinoline ring. Furthermore, using the pulsed Fourier transform technique,[10] a nuclear Overhauser effect (NOE) was observed with **7a** but not with 8. Irradiation of the 3-methyl substituent of **7a** resulted in a 19% enhancement in the integral of the signal for the adjacent ring proton, H-2, while irradiation of the methyl group in 8 increased the integral of H-1 by only 2%.

By establishing the structure of **7a** unequivocally, the structure assignment for **7b** was then made by a comparison of its ^{1}H NMR spectrum, and particularly the ^{1}H NMR parameters of the pyrrole ring proton, with that of compound **7a.**



A second indication that the structure assignment for **7a** was correct was obtained when irradiation of a degassed, methanolic solution of **7a,** in the presence of a trace of iodine, resulted in a photocyclization reaction yielding compound **9a** in 8% isolated yield. The structural assignment for **9a** was based on the expected changes in both the uv and NMR spectra for this product as compared to those of the starting material, **7a** (see Experimental Section).

Surprisingly, **7b** failed to undergo photocyclization to **9b** under analogous reaction conditions. An alternate attempt to prepare **9b** was also unsuccessful. This involved the treatment of **1b** with acetic anhydride and o-nitrophenylacetylene to furnish the 1-(*o*-nitrophenyl)pyrrolo[2,1-*a*]isoquinoline (**7c**). Subsequent catalytic hydrogenation of the nitro group provided the amine **7d.** Several attempts were then made to convert **7d** into **9b** via a Pschorr cyclization reaction, but all efforts were unsuccessful. Examination of the reaction mixture after diazotization and treatment with copper powder failed to show the characteristic ultraviolet and ^{1}H NMR spectra exhibited by the analogous, cyclized compound **9a.**



9a, R = H
b, R = OCH_3

Experimental Section

Melting points were taken on a Thomas-Hoover Uni-Melt capillary apparatus which was calibrated against known standards. Ultraviolet spectra were recorded in CH_3OH solutions on a Beckman DK-2A spectrometer; infrared spectra were determined in $CHCl_3$ solutions or KBr disks on a Beckman IR-12 spectrometer; ^{1}H NMR spectra were obtained on a Varian Associates A-60, T-60, or HA-100 spectrometer from $CDCl_3$ or $(CD_3)_2SO$ solutions using tetramethylsilane as an internal standard; mass spectra were run on an A.E.I. MS-30. Microanalyses were performed by the Searle Laboratories Microanalytical Department.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (1b). A solution consisting of β-(3,4-dimethoxyphenyl)ethylamine (36.25 g, 0.20 mol), glyoxylic acid hydrate (29.6 g), concentrated hydrochloric acid (50 ml), and water (500 ml) was stirred and warmed to 75° for 3 hr and then allowed to stand at 25° for 18 hr. The resultant yellow solution was neutralized with 5 *N* sodium hydroxide solution until pH 5.0 was reached (163.8 ml required, pH meter used). The mixture was then cooled in an ice–water bath and filtered, and the solid that had been collected was washed with a small amount of cold water. A colorless solid (9.60 g, 20%) was obtained: mp 252–257°; ir (KBr) ν_{NH_2} 2250–2700 cm^{-1}, ν_{CO} 1610 cm^{-1}; ^{1}H NMR (C_5D_5N–D_2O mixture) δ 3.10 (t, CH_2, J = 6 Hz), 3.71 (t, CH_2, J = 6 Hz), 3.91 and 4.03 (s, OCH_3), 6.67 and 7.53 (s, aromatic protons).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.59; H, 6.35; N, 5.83.

The above experiment was repeated several times after this initial reaction had been carried out, and the yield of the product, **1b,** obtained ranged from 0 to 20%.

1-(2′-Methyl-1′-propenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3). The dihydroisoquinoline salt **2** (135.2 g, ca. 0.4 mol), obtained by the Bischler–Napieralski reaction of *N*-1β-(3,4-dimethoxyphenyl)ethyl]-3-methyl-2-butenamide with phosphorous oxychloride in benzene,[7] was dissolved in methanol (1300 ml) and cooled to 5°. A 20% sodium hydroxide in methanol solution was added until the pH of the resultant mixture was >10 (ca. 400 ml was required). Sodium borohydride (50.4 g) was then added to the alkaline mixture in small portions, and the temperature was kept at 5° throughout this addition. The reaction mixture was stirred overnight at room temperature, and then evaporated to dryness in vacuo. Water (1 l.) was added to the residue and the resultant alkaline mixture was extracted with methylene chloride (4 × 400 ml). The combined CH_2Cl_2 extract was washed with brine (2 × 400 ml), dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo. The yellow oil that remained was taken up in dry ether (1500 ml) and treated with a solution of HCl in isopropyl alcohol to form a cream-colored, crystalline hydrochloride salt (87.6 g, 77%), mp 223–229°. Recrystallization from acetonitrile furnished a colorless, crystalline solid: mp 230–231°; ir ($CHCl_3$) ν_{NH} 2400–2810 cm^{-1}, $\nu_{C=C}$ 1620 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] δ 1.90 and 2.00 (s, CH_3), 3.00–3.80 (m, 2 CH_2), 3.81 and 3.86 (s, OCH_3), 4.95–5.65 (m, 2 CH), 6.50 and 6.61 (s, aromatic protons).

Anal. Calcd for $C_{15}H_{21}NO_2$·HCl: C, 63.48; H, 7.81; N, 4.94; Cl, 12.49. Found: C, 63.22; H, 7.95; N, 5.11; Cl, 12.64.

1-(2′-Methyl-1′-propenyl)-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4). A mixture of **3** (14.2 g, 0.05 mol), pyridine (100 ml), and methylene chloride (100 ml) was stirred, cooled to 10°, and treated with acetic anhydride (25 ml). The temperature of the reaction mixture was allowed to return to 25°, and kept at that temperature overnight (16 hr). The reaction mixture was poured into a slurry of concentrated hydrochloric acid (50 ml) and ice (300 ml). After the resultant two-phase mixture was separated, the aqueous acidic layer was extracted further with methylene chloride (2 × 100 ml). The combined CH_2Cl_2 extract was washed cautiously with a 5% $NaHCO_3$ solution (foaming) and then dried (Na_2SO_4). Removal of the solvent in vacuo and trituration of the residue with hexane afforded a colorless solid (12.0 g, 83%): mp 104–106.5°; ir ($CHCl_3$) $\nu_{C=O}$ 1670 cm^{-1}, $\nu_{C=C}$ 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 and 2.05 (s, CH_3), 2.13 (s, CH_3), 5.00–5.50 (m, 2 CH).

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.26; H, 7.96; N, 4.46.

2-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (5). A solution consisting of **4** (14.45 g, 0.05 mol), potassium carbonate (27.65 g, 0.20 mol), *tert*-butyl alcohol (400 ml), and water (400 ml) was vigorously stirred in a creased three-necked flask using a mechanical stirrer. To this stirred mixture, two solutions, one consisting of potassium permanganate (0.8 g, 0.005 mol) in water (50 ml) and the other comprised of sodium metaperiodate (42.8 g, 0.20 mol) in water (300 ml), were added at room temperature simultaneously over a 1-hr period. The reaction mixture was then stirred for an additional 8 hr and then allowed to

stand at room temperature overnight. Isopropyl alcohol (75 ml) was added, and the reaction mixture was stirred at 25° for 1 hr and then diluted further with water (600 ml). Acetic acid (100 ml) was added in small portions (caution—foaming) and the resultant acidic mixture was extracted with chloroform (2 × 500 ml). The organic extract was washed with a 5% sodium thiosulfate solution (500 ml) and then with brine (500 ml) and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was triturated with ether and yielded a yellow solid. Recrystallization of this solid from ethyl acetate furnished a light-tan powder (8.0 g, 57%): mp 207.5–210°; ir ($CHCl_3$) ν_{OH} 3300–3000 cm^{-1}, $\nu_{C=O}$ 1760, 1725, 1650 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 2.10 (s, CH_3), 2.83 (t, CH_2, J = 6 Hz), 3.73 (t, CH_2, J = 6 Hz), 3.75 (s, OCH_3), 5.60 (s, CH), 6.83 and 7.08 (s, aromatic protons).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.00; H, 6.23; N, 5.01.

Dimethyl 3-Methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (6a). A mixture consisting of **1a** (5.3 g, 0.03 mol), dimethyl acetylenedicarboxylate (5.70 g, 0.04 mol), and acetic anhydride (150 ml) was stirred and heated to 90°. Within 15 min, an orange solution had developed and carbon dioxide evolution had ceased. This solution was cooled and evaporated to dryness in vacuo. The residue was recrystallized from methanol, yielding a cream-colored, crystalline solid (5.55 g, 62%): mp 118–119°; ir ($CHCl_3$) $\nu_{C=O}$ 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50 (s, CH_3), 2.98 (t, CH_2, J = 6 Hz), 3.76 (t, CH_2, J = 6 Hz), 3.80 and 3.90 (s, OCH_3), 7.00–7.60 (m, aromatic protons).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.22; H, 5.81; N, 4.65.

Dimethyl 3-Methyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (6b). The procedure just described for compound **6a** was repeated using **1b** (3.55 g, 0.015 mol), dimethyl acetylenedicarboxylate (3.10 g, 0.022 mol), and acetic anhydride (75 ml). A colorless, crystalline solid was obtained on recrystallization of the crude product from methanol (4.20 g, 78%): mp 173–174°; ir ($CHCl_3$) $\nu_{C=O}$ 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (s, CH_3), 2.95 (t, CH_2, J = 6 Hz), 3.81 and 3.90 (s, OCH_3, 12 protons), 3.91 (t, CH_2 J = 6 Hz), 6.71 and 7.46 (s, aromatic protons).

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.37; H, 5.86; N, 3.81.

Repeating this experiment, but replacing **1b** with **5** (4.15 g, 0.015 mol), resulted in the isolation of product **6b** in 65% yield.

1-Phenyl-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (7a). A mixture composed of **1a** (3.55 g, 0.02 mol), phenylacetylene (4.10 g, 0.04 mol), and acetic anhydride (100 ml) was stirred and heated to 80° for 30 min. The resultant solution was cooled and evaporated to dryness in vacuo. Recrystallization of the residue from methanol provided light-tan needles (3.50 g, 69%): mp 120–122°; λ_{max} (CH_3OH) 319 nm (ϵ = 14,000), 259 (13,500); ^1H NMR ($CDCl_3$) δ 2.28 (s, CH_3), 3.03 (t, CH_2, J = 6 Hz), 3.91 (t, CH_2, J = 6 Hz), 6.00 (q, pyrrole H, J_{H,CH_3} = 1.0 Hz), 6.83–7.60 (m, aromatic protons); mass spectrum m/e 259 (M^+).

Anal. Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 87.61; H, 6.56; N, 5.25.

1-Phenyl-3-methyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (7b). The procedure just described for compound **7a** was repeated using either compound **1b** (3.55 g, 0.015 mol) or compound **5** (5.6 g, 0.02 mol), phenylacetylene (3.05 g, 0.03 mol), and acetic anhydride (100 ml). Recrystallization of the crude product from ethanol furnished an ivory-colored solid (3.30 g, 69% from **1b** and 4.60 g, 72% from **5**): mp 174–176°; ^1H NMR ($CDCl_3$), δ 2.28 (s, CH_3), 3.03 (t, CH_2, J = 6 Hz), 3.90 (t, CH_2, J = 6 Hz), 3.43 and 3.86 (s, OCH_3), 6.00 (q, pyrrole H, J_{H,CH_3} = 1.1 Hz), 6.70 and 6.88 (s, aromatic protons), 7.16–7.66 (m, aromatic protons).

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.73; H, 6.62; N, 4.34.

2-Phenyl-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (8). α-Bromopropiophenone (10.65 g, 0.05 mol) was added in dropwise portions over a 15-min period at room temperature to a stirred mixture of 1-methyl-3,4-dihydroisoquinoline[11] (7.25 g, 0.05 mol) and sodium bicarbonate (12.6 g) in ethanol (130 ml). The reaction mixture was heated to reflux for 3 hr, then cooled to 5° and filtered. The solid collected was washed with ethanol (100 ml) and water (200 ml) and then recrystallized from 1-butanol to yield a light-yellow, crystalline solid (2.3 g, 18%): mp 171–173°; λ_{max} (CH_3OH) 314 nm (ϵ 15,500), 240 (16,300); ^1H NMR ($CDCl_3$) δ 2.36 (s, CH_3), 3.03 (t, CH_2, J = 6 Hz), 3.96 (t, CH_2, J = 6 Hz), 6.68 (s, pyrrole proton), 7.00–7.70 (m, aromatic protons).

Anal. Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 88.13; H, 6.81; N, 5.51.

6-Methyl-4,5-dihydroindolizino[1,7,8,8a-*a,b,c*]phenanthrene (9a). A solution of **7a** (1.000 g, 3.8 mmol) in methanol (300 ml) containing iodine crystals (0.1 g) was degassed and irradiated, under a nitrogen atmosphere with constant stirring, by using a medium-pressure, 450-W Hanovia lamp. A Vycor filter was used in this photochemical experiment; no reaction was observed to occur when a Pyrex filter was used. After 20 hr, additional iodine (0.1 g) was added, and the reaction mixture was irradiated for another 20 hr. Throughout this experiment, the reaction mixture was monitored by TLC (15% ethyl acetate–85% cyclohexane/phosphomolybdic acid spray). After 40 hr, only a trace of **7a** remained (R_f 0.39) along with the product (R_f 0.31). The methanolic solution was filtered and evaporated to dryness in vacuo, and the residue was redissolved in benzene (200 ml). The brown benzene solution was washed with a 5% sodium sulfite solution (3 × 100 ml) and water (100 ml) and then dried ($MgSO_4$). Removal of the solvent in vacuo left a brown semisolid residue which crystallized on standing overnight at room temperature. Recrystallization from ethanol afforded an off-white powder (0.077 g, 8%): mp 151–155°; λ_{max} (MeOH) 293 nm (ϵ 16,000), 262 (65,000), 254 (44,000); ^1H NMR ($CDCl_3$, 100 MHz) δ 2.48 (s, CH_3), 3.44 (t, CH_2, J = 6 Hz), 4.20 (t, CH_2, J = 6 Hz), 6.69 (broad s, pyrrole H), 7.20–8.66 (m, aromatic protons); mass spectrum m/e 257 (M^+).

Anal. Calcd for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.28; H, 6.12; N, 5.28.

Examination of the ethanolic mother liquor of **9a** indicated the presence of additional product contaminated with unreacted starting material, **7a**. Several attempts were made to obtain additional pure product by subjecting the mother liquor to preparative thin layer or dry column chromatography. Complete separations, however, could not be achieved.

The analogous experiment was conducted using **7b** in an attempt to prepare **1,2-dimethoxy-4,5-dihydro-6-methylindolizino[1,7,8,8a-*a,b,c*]phenanthrene (9b).** After 40 hr of irradiation, examination of the reaction mixture by TLC showed only the presence of unreacted **7b**. Evaporation of this photolysate to dryness and examination of the residue by uv and ^1H NMR spectroscopy confirmed the presence of only unreacted **7b**.

1-(*o*-Nitrophenyl)-3-methyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (7c). Using the reaction conditions described for the preparation of **7a**, a mixture of **1b** (4.75 g, 0.020 mol), *o*-nitrophenylacetylene[12] (3.25 g, 0.022 mol), and acetic anhydride (100 ml) was stirred and heated to 90° for 1 hr. The residue obtained, by using the previously described work-up procedure, was recrystallized from 1-butanol and a red-colored powder, compound **7c**, was isolated (6.0 g, 82%): mp 190–191°; ^1H NMR ($CDCl_3$) δ 2.25 (s, CH_3), 2.96 (t, CH_2, J = 6 Hz), 3.36 and 3.80 (s, OCH_3), 3.90 (t, CH_2, J = 6 Hz), 5.90 (q, pyrrole H, J_{H,CH_3} = 1.0 Hz), 6.45 and 6.68 (s, aromatic protons), 7.10–7.90 (m, aromatic protons).

Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.21; H, 5.72; N, 7.79.

1-(*o*-Aminophenyl)-3-methyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (7d). A solution of **7c** (3.64 g, 0.01 mol) in 1,2-dimethoxyethane (50 ml) was treated with platinum oxide catalyst (364 mg) and the mixture was hydrogenated at room temperature and atmospheric pressure on a Parr shaker apparatus for 24 hr. The reaction mixture was then filtered and evaporated to dryness in vacuo, and the solid residue was recrystallized from ethanol, yielding a light-orange solid (2.0 g, 60%): mp 177–179°; ir ($CHCl_3$) μ_{NH_2} 3480, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) similar spectrum as described for **7c**, except for the presence of a broad exchangeable signal centered at δ 3.52 and integrating for two protons.

Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 74.95; H, 6.67; N, 8.21.

Attempts to cyclize **7d** into **9b** using a Pschorr cyclization reaction were unsuccessful. These efforts involved diazotization of a solution of **7d** (668 mg, 2 mmol) in concentrated sulfuric acid (20 ml)–water (50 ml) with sodium nitrite (152 mg, 2.2 mmol) in water (10 ml), followed by heating the reaction mixture with copper powder. Work-up of this reaction furnished tarry residues which did not exhibit the characteristic uv absorptions in the 250–260-mμ region (see uv data on **9a**).

Acknowledgment. The author wishes to thank Dr. Roy Bible, Ms. Patricia Green, and Ms. Elisabeth Hajdu for conducting the NOE experiments, Mr. Michael Scaros for

the catalytic hydrogenation, and Dr. George Lenz for the helpful discussions and assistance with the photochemical reactions described.

Registry No.—**1a,** 41034-52-0; **1b,** 41143-95-7; **2,** 53957-21-4; **3,** 53927-32-5; **4,** 53927-33-6; **5,** 13326-60-8; **6a,** 53927-34-7; **6b,** 53927-35-8; **7a,** 53927-36-9; **7b,** 53927-37-0; **7c,** 53927-38-1; **7d,** 53927-39-2; **8,** 53957-18-9; **9a,** 53927-40-5; β-(3,4-dimethoxyphenyl)ethylamine, 120-20-7; glyoxylic acid, 298-12-4; dimethyl acetylenedicarboxylate, 762-42-5; phenylacetylene, 536-74-3; α-bromopropiophenone, 2114-00-3; 1-methyl-3,4-dihydroisoquinoline, 2412-58-0; *o*-nitrophenylacetylene, 16433-96-8.

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Synthesis of Substituted 2*H*-1,3-Oxazine-2,6-diones by Reaction of Trimethylsilyl Azide with Maleic Anhydrides[1]

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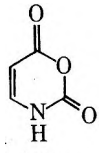
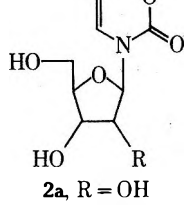
Received October 23, 1974

The synthesis of 4-bromo-, 4-chloro-, 4,5-dichloro-, 4-fluoro-, and 4-methyl-2*H*-1,3(3*H*)-oxazine-2,6-dione, as well as an improved synthesis of 2*H*-1,3(3*H*)-oxazine-2,6-dione, by reaction of trimethylsilyl azide with the corresponding maleic anhydride is described. This route is superior to other methods for preparation of 4-substituted oxazinediones. N-Methylation of the oxazinedione ring may be readily accomplished with dimethyl sulfate buffered by sodium bicarbonate.

The heterocycle derived from uracil by isosteric replacement of the imidic nitrogen, 2*H*-1,3(3*H*)-oxazine-2,6-dione or oxauracil (**1a**), was first prepared by Rinkes[2] in 1927 by sodium hypochlorite oxidation of maleimide. In 1972 this laboratory reported an alternate preparation of **1a** by reaction of maleic anhydride with trimethylsilyl azide.[3] Shortly thereafter, reports by Škoda and coworkers[4] and Bobek and coworkers[5] of the growth inhibitory properties of **1a** vs. *E. coli* and L1210 leukemia cells in vitro stimulated a renaissance of interest in the oxazinedione ring system. The *N*-riboside **2a** had approximately the same activity as **1a** in



1a

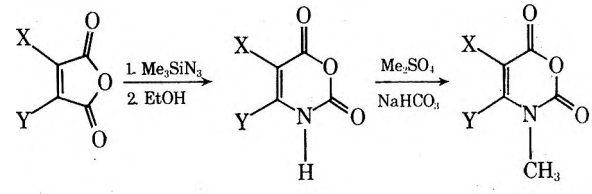


2a, R = OH
3a, R = H

inhibiting growth of L5178Y cells in culture,[6] while oxathymine **1i** was less inhibitory in microbial and tumor cell systems, and the deoxyriboside **3a** was about 1000 times more potent than **1a** in inhibiting *S. faecium* growth.[5] 5-Fluorooxauracil (**1h**) is active vs. the L1210 cell line, but toxic.[5b] The Škoda group has recently reported on the mechanism of inhibition of *E. coli* growth by **1a,** and detailed conditions of the hydrolytic fission of the oxazinedione ring.[7]

Our interest in the regioselective synthesis of alkyl- and halooxazinediones as agents against neoplastic and protozoan disease, particularly malaria, leads us to detail improved synthetic pathways to these heterocycles.

Synthesis. Oxauracil (**1a**) was first prepared by Rinkes by oxidation of maleimide[2] with basic aqueous sodium hypochlorite. Similar oxidation of citraconimide to 5-methyl-2*H*-1,3(3*H*)-oxazine-2,6-dione (oxathymine) has been reported.[5] Other syntheses of the ring system in **1** involve cyclization of the appropriate β-(ethoxycarbonylamino)-acrylic acid to the oxazinedione[5] or lead tetraacetate oxidation of maleic acid monoamide.[7] In a preliminary report[3] we synthesized **1a** by reaction of trimethylsilyl azide with maleic anhydride in benzene solvent.



1 **4**

The original trimethylsilyl azide–maleic anhydride reaction has been exteded to methyl- and halooxazinediones and appears to be the method of choice. Since the oxazinedione ring undergoes facile thermal decarboxylative polymerization to yield polyamides[8] and suffers hydrolytic ring fission at 25° in either acidic or basic media yielding formylacetic acid,[7] any synthetic procedure must be carried out at moderate temperature under essentially neutral conditions. In our hands, the Rinkes hypochlorite oxidation of either maleimide[2] or citrazonimide[5a] did not yield the corresponding oxazinedione even after several attempts in which the pH was carefully controlled.

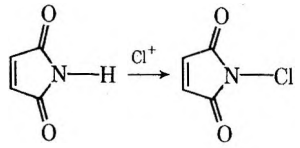
Table I
Methyl- and Halo-Substituted 2*H*-1,3(3*H*)-Oxazine-2,6-diones from Trimethylsilyl Azide and Substituted Maleic Anhydrides

Compd	X	Y	Yield, %	Procedure[a]	Reaction time, hr	δ, ppm C_4-H	δ, ppm C_5-H
1a	H	H	69	A	1.5	7.52	5.59
1b	H	CH_3	33	A	3.0		5.38
1c	CH_3	CH_3	0	B			
1d	H	Br	30	B	6.0		5.87
1e	H	Cl	57[b]	B	4.0		5.84
1f	Cl	Cl	38	A	6.0		
1g	H	F	10	A	0.75		5.36
1h	F	H		*c*			
1i	CH_3	H		*d*		7.57	
4a	H	H	71	C	20	7.75	5.65
4b	H	CH_3	64	C	22		5.60

[a] Procedure A, $CHCl_3$ solution (see Experimental Section); procedure B, neat (see Experimental Section); procedure C, dimethyl sulfate–sodium bicarbonate in acetone (see Experimental Section). [b] Commercially available 70% azeotrope of chloromaleic anhydride–maleic anhydride was employed. [c] See ref 5b. [d] See ref 5a.

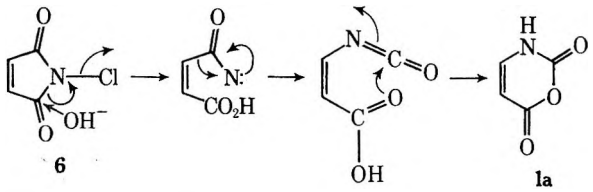
The synthetic utility of our procedure is that it permits a one-step regioselective synthesis of 4-substituted oxazinediones **1** in acceptable yields from commercially available maleic anhydrides (see Table I).

The Rinkes hypohalite oxazinedione procedure probably proceeds via the intermediacy of *N*-chloromaleimide (**6**), which then suffers hydrolytic fission and rearrangement to **1a**. We have isolated **6** by treatment of maleimide with ei-



6

ther sodium or calcium hypochlorite in aqueous acetic acid. Indeed, **6** does rearrange to **1a** in aqueous sodium bicarbonate solution. We have not maximized the yield for this procedure; however, it has merit as a possible route to 5-substituted oxazinediones, as Bobek[5] has converted citraconimide into oxathymine by hypochlorite oxidation.

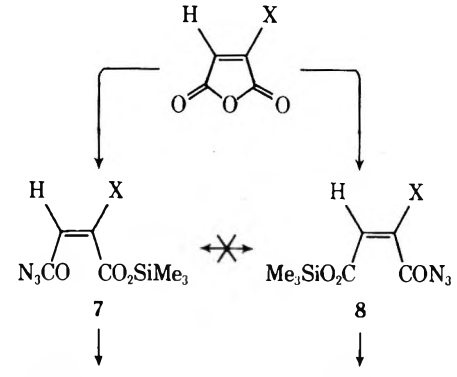


6 **1a**

Spectral Analysis. The oxazinedione ring system can readily be identified by ir or ^{1}H NMR spectral analysis. A characteristic ir spectrum has two strong sharp carbonyl stretching absorptions at 1815–1780 cm^{-1} (C_6 carbonyl) and at 1755–1710 (C_2 carbonyl) together with a strong absorption at 1670–1602 cm^{-1} (C_4–C_5 alkene stretch). A broad absorption in the 3400–3100 cm^{-1} range for the N–H stretch was also visible. The characteristic ^{1}H NMR resonances for the C_5 proton were in the 5.38–5.87 ppm region while the C_4 proton (β to the C_6 carbonyl) resonated at 7.52 ppm in **1** and at 7.57 ppm in 5-methyl-2*H*-1,3(3*H*)-oxazine-2,6-dione (oxathymine).[4] Data are summarized in Table I above. Dominant features of the mass spectra are a moderate to strong molecular ion together with a prominent M − 44 peak corresponding to extrusion of carbon dioxide from the molecular ion.

N-Methylation of 1a,b. Introduction of functionalities at nitrogen in the oxazinedione ring system has proved quite difficult due to the previously described instability of the ring to hydrolysis in acidic or basic media. Attempts to N-methylate the ring failed with methyl iodide and methyl fluorosulfonate, apparently due to generation of acidic hydrogen iodide and fluorosulfonic acid as the reactions proceeded. However, Fieser[9] describes the mild alkylating system acetone–dimethyl sulfate–potassium carbonate for methylation of plant phenols. We found that a modified procedure employing the mild buffe sodium bicarbonate resulted in N-methylated oxazinediones in 65–70% yields. The chemical shift of the methyl singlet was consistent with N- rather than O-alkylation, as was the infrared spectrum where both characteristic oxazinedione carbonyl-stretching frequencies at 1780 and 1720 cm^{-1} were still present.

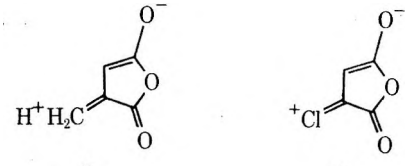
Orientation of Nitrogen Insertion into the Substituted Maleic Anhydrides. Examination of the product distribution given in Table I indicates that 4-substituted products are produced preferentially over 5-substituted oxazinediones. While the exact mechanism for these transformations is not certain, it seems highly probable that the initial nucleophilic attack of azide at an anhydride carbonyl determines the regiochemistry of product oxazinedione;[10] i.e., **7** and **8** do not interconvert.[11]



7 **8**

5-substituted product 4-substituted product

Obviously, steric interference by the substituent is not product determining since the more hindered carbonyl is preferentially attacked, even in the case of the bulky bromine group. Electronic factors must be rate determining for these systems. Although little substantive information is available concerning regioselectivity of nucleophilic attack at substituted maleic anhydrides, the azide should attack the most electropositive carbonyl, i.e., the carbonyl α to the substituent. For the halo substituents simple inductive electron withdrawal from the proximate carbonyl by the electronegative halogens could be invoked. However, this rationalization breaks down for the methyl substituent since inductively this electron-releasing group should make the α-carbonyl less electropositive. It appears that a conjugative interaction between the substituent and the double bond must be invoked, involving canonical resonance forms such as **5**. This resonance interaction feeds electron density



5a **5b**

to the carbonyl β to the substituent carbonyl making it less susceptible to nucleophilic attack. For the methyl group a hyperconjugative type interaction **5a** could be involved.

This effect is analogous to the similar orientation effects observed for methyl- and halo-substituted aromatic rings. The nonreactivity of dimethylmaleic anhydride under our reaction conditions is also consistent with such an interaction. For this compound both carbonyls would possess added electron density, making nucleophilic attack by an azide a higher activation energy process. Electron supply via **5b** must, in the case of dichloromaleic anhydride (**1f**), be overridden by inductive electron withdrawal, since **1f** reacts smoothly.

Further mechanistic study of this synthetic procedure will be the subject of another communication.

Experimental Section[12]

General Comments. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 727 infrared spectrophotometer. Proton magnetic resonance spectra were obtained with a Varian XL-100-15 spectrometer using an internal tetramethylsilane standard. Elemental analyses were pformed by Galbraith Laboratories, Knoxville, Tenn. All solvents were reagent grade and dried over Linde 4A molecular sieves before use. The fluoromaleic anhydride was synthesized according to the literature procedure.[13] Trimethylsilyl azide was purchased from Petrarch Systems Inc., Levittown, Pa.

Synthesis of 2*H*-1,3(3*H*)-Oxazine-2,6-diones. Method A. Chloroform Procedure. A solution of the appropriately substituted maleic anhydride in chloroform was refluxed with a slight excess of trimethylsilyl azide until gas evolution slowed. Cooling of the solution of 0° and hydrolysis with absolute ethanol gave the desired product which was washed with chloroform. Purifications were effected by recrystallization from boiling ethyl acetate or by sublimation.

The following oxazinediones were synthesized, with slight modification, by the above procedure.

2*H*-1,3(3*H*)-Oxazine-2,6-dione (1a). Maleic anhydride (4.8 g, 49 mmol) in deuteriochloroform (15 ml) was refluxed with trimethylsilyl azide (6.0 g, 52 mmol) for 1 hr resulting in evolution of 900 ml of gas. ^{1}H NMR (CH_3CN internal standard) showed resonances consistent with a silylated oxazinedione intermediate at δ 0.43 [s, 9, $(CH_3)_3Si$–], 5.59 (d, 1, J = 7.5 Hz, C_5-H), and 7.29 (d, 1, J = 7.5 Hz, C_4-H). Dilution with 20 ml of benzene and hydrolysis with ethanol gave 3.81 g (69%) of off-white powder: mp 158–158.5° (lit.[3] mp 158–159° dec; ir (mull) 3300 (m), 3150 (m), 3120 (m), 1790 (s), 1710 (vs), 1635 (s), 1200 (s), 1105 (s), 1055 (m), 980 (s) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.56 (d, 1, J = 7.5 Hz, C_5-H), 7.52 (d, 1, J = 7.5 Hz, C_4-H), 10.75 (broad, 1, NH); MS (70 eV) *m/e* (rel intensity) 113 M^+ (58), 69 M – CO_2 (100), 43 $HNCO^+$ (52), and 44 $CO_2{\cdot}^+$ (52).

4-Methyl-2*H*-1,3(3*H*)-oxazine-2,6-dione (1b). Citraconic anhydride (56.0 g, 0.5 mol) was refluxed with trimethylsilyl azide (61.0 g, 0.53 mol) in 75 ml of chloroform for 5 hr. Work-up as described in procedure A above gave 21.0 g (33%) of microcrystalline white powder, mp 140–5° dec. Crystallization from ethyl acetate gave 10.6 g of **1b**: mp 176.5°; ir (mull) 3300 (m), 3125 (m), 1790 (s), 1710 (s), 1640 (s), 1040 (m), 970 (m) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.08 (s, 3, C_4-methyl), 5.38 (s, 1, C_5-H), 11–12 (broad, 1, N-H); MS (70 eV) *m/e* (rel intensity) 127 M^+ (57.2), 83 M – CO_2 (46), 68 M – $HNCO_2$ (46), 44 $CO_2{\cdot}^+$ (41.3), 42 (100).

Anal. Calcd for $C_5H_5NO_3$: C, 47.25; H, 3.96; N, 11.02. Found: C, 47.37; H, 3.98; N, 11.16.

4-Fluoro-2*H*-1,3(3*H*)-oxazine-2,6-dione (1g). Fluoromaleic anhydride (2.9 g, 25 mmol) in 10 ml of chloroform was stirred with trimethylsilyl azide (3.45 g, 30 mmol) for 10 min and then refluxed for 0.5 hr. Cooling to room temperature and hydrolysis with 1.5 ml of absolute ethanol gave 0.34 g (10–) of off-white powder: mp 113–114° dec; ir (mull) 3200 (m), 1800 (s), 1750 (s), 1670 (s), 1060 (m), 990 (m), 810 (m) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 5.36 (d, 1, J = 7 Hz, C_5-H), 8.5 (broad, 1, NH).

Sublimation [75° (0.02 mmHg)] gave an analytical sample, mp 104–105.5° dec.

Anal. Calcd for $C_4H_2FNO_3$: C, 36.67; H, 1.54; F, 15.00; N, 10.69. Found: C, 36.37; H, 1.62; F, 15.04; N, 10.65.

4,5-Dichloro-2*H*-1,3(3*H*)-oxazine-2,6-dione (1f). Dichloromaleic anhydride (8.35 g, 50 mmol) in 20 ml of *p*-dioxane was refluxed with trimethylsilyl azide (5.8 g, 50 mmol) for 5 hr; 1.05 l. of gas were evolved. The solution was cooled to room temperature, filtered, treated with 3.5 ml of absolute ethanol, and diluted with 50 ml of chloroform. Cooling to −20° gave 3.74 g (38%) of off-white crystals, mp 209–210° dec. Recrystallization from 1:1 ethyl acetate–hexane gave 2.2 g of light yellow crystals: mp 204–206° dec; ir (mull) 3100 (w), 1815 (s), 1755 (s), 1605 (m), 995 (m), 895 (m) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.9 (broad, NH).

Anal. Calcd for $C_4HCl_2NO_3$: C, 26.40; H, 0.56; Cl, 38.97; N, 7.70; O, 26.37. Found: C, 26.48; H, 0.57; Cl, 39.07; N, 7.61; O, 26.28.

Method B. Neat Procedure. Chloro- and bromomaleic anhydrides were found to react sluggishly when treated with trimethylsilyl azide by procedure A above; therefore they were treated without solvent with a sizable excess of trimethylsilyl azide. The procedure consists of gently heating the reactants until a moderate gas evolution occurs. The pot is cooled when necessary to moderate the reaction. A nitrogen evolution rate of approximately 1 l./hr is preferable. Overheating the solution must be avoided as a vigorous and uncontrollable reaction will ensue resulting in intractable tars. After approximately the stoichiometric amount of nitrogen has been evolved, the reaction is cooled to room temperature, diluted with benzene, and hydrolyzed with a stoichiometric amount of absolute ethanol and the product purified by vacuum sublimation or recrystallization.

4-Chloro-2*H*-1,3(3*H*)-oxazine-2,6-dione (1e). Chloromaleic anhydride (6.0 g, 70% by weight, 32 mmol) and trimethylsilyl azide (11.0 g, 95 mmol) were heated cautiously to 70–90° for 1 hr. Dilution with 40 ml of benzene and work-up as described above gave 2.7 g of tan powder, mp 133.5–134.5° dec. Sublimation at 100° (0.02 mmHg) afforded 1.43 g (29%) of white powder, mp 135–137° dec. Crystallization from ethyl acetate gave white needles, 0.40 g: mp 139–140° dec; ir (mull) 3120 (m), 1790 (s), 1725 (s), 1615 (s), 1120 (m), 980 (m) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 5.84 (s, C_5-H), 11.0 (broad, NH).

Anal. Calcd for $C_4H_2ClNO_3$: C, 32.57; H, 1.37; N, 9.49; Cl, 24.03. Found: C, 32.66; H, 1.42; N, 9.56; Cl, 24.11.

4-Bromo-2*H*-1,3(3*H*)-oxazine-2,6-dione (1d). Bromomaleic anhydride (8.85 g, 50 mmol) and trimethylsilyl azide (8.9 g, 77 mmol) reacted at 70–90° for 1 hr as described above. Work-up as described above followed by cooling to 0° gave 3.0 g (30%) of tan powder containing approximately 10% of the isomeric 5-bromo isomer. Pure material may be obtained by repeated recrystallization from hot ethyl acetate: mp 149–151° dec; ir (mull) 3175 (m), 1780 (s), 1602 (s) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.87 (s, 1, C_5-H), 11.0 (broad, 1, NH).

Anal. Calcd for $C_4H_2BrNO_3$: C, 25.03; H, 1.05; Br, 41.63; N, 7.30; O, 25.0. Found: C, 25.02; H, 1.00; Br, 41.48; N, 7.37; O, 25.09.

Method C. Methylation Procedure. This procedure is a modification of Fieser's procedure[9] for methylation of plant phenols. The oxazinedione is refluxed in dry acetone with a slight molar excess of dimethyl sulfate and sodium bicarbonate buffer. Reactions may be followed by TLC. Generally 3–24 hr are required for complete reaction. The reactions are then filtered and the acetone is removed under reduced pressure. The semisolid residues are triturated with hot ethyl acetate and cooled, giving the 3-methylated derivative.

3-Methyl-2*H*-1,3(3*H*)-oxazine-2,6-dione (4a). 2*H*-1,3(3*H*)-Oxazine-2,6-dione (2.5 g, 22 mmol) in acetone (65 ml) was refluxed under nitrogen with dimethyl sulfate (3.2 g, 25 mmol) and sodium bicarbonate (2.5 g, 30 mmol) for 20 hr. Work-up as described above gave 2.0 g (71%) of **2a**, white crystals: mp 110–111° dec; ir ($CHCl_3$) 3130 (m), 1790 (s), 1745 (s), 1715 (s), 1640 (s), 1360 (m) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.2 (s, 3, NCH_3), 5.65 (d, 1, J = 7.5 Hz, C_5-H), 7.75 (d, 1, J = 7.5 Hz, C_4-H); MS (70 eV) *m/e* (rel intensity) 127 M^+ (100), 83 M – CO_2 (132), 55 M – C_2O_3 (109), 44 $CO_2{\cdot}^+$ (70), 42 CON^+ (190).

Anal. Calcd for $C_5H_5NO_3$: C, 47.25; H, 3.96; N, 11.02. Found: C, 47.01; H, 3.90; N, 10.91.

(3,4)-Dimethyl-2*H*-1,3(3*H*)-oxazine-2,6-dione (4b). 4-Methyl-2*H*-1,3(3*H*)-oxazine-2,6-dione (1.7 g, 13.3 mmol) in acetone (40 ml) with dimethyl sulfate (1.9 g, 15 mmol) and sodium bicarbonate (1.5 g, 18 mmol) was refluxed under nitrogen for 22 hr. Work-up as described above gave 1.2 g (64%) of **4b**, white crystals: mp 83–85° dec; ir ($CHCl_3$) 3120 (m), 2960 (m), 1780 (s), 1720 (s), 1630 (s), 1370 (m) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.4 (d, 3, J = 1 Hz, CH_3), 3.4 (s, 3, N–CH_3), 5.6 (q, 1, J = 1 Hz, C_5-H).

Anal. Calcd for $C_6H_7NO_3$: C, 51.07; H, 4.99; N, 9.92. Found: C, 50.90; H, 5.23; N, 9.78.

***N*-Chloromaleimide (6).** To a stirred solution of maleimide (2.43 g, 25 mmol) in 40 ml of 53% (w/v) aqueous acetic acid at 0° was added 35 ml of fresh 5.25% aqueous sodium hypochlorite [or pulverized calcium hypochlorite (4.3 g, 30 mmol)] over a period of 10 min. After 0.5 hr, the white precipitate was collected, washed

with ice-cold H_2O, and sucked dry, 1.9 g (58%): mp 101–103.5° dec; [11] ir (mull) 3110 (m), 1765 (m), 1710 (s), 1635 (m), 1320 (s), 1270 (s), 865 (m), 850 (m) cm^{-1}.

2*H*-1,3(3*H*)-Oxazine-2,6-dione (1a). To a stirred dispersion of *N*-chloromaleimide (250 mg, 1.9 mmol) in 10 ml of H_2O at 0° was added dropwise over a period of 0.25 hr a solution of $NaHCO_3$ (180 mg, 2.1 mmol) in 5.0 ml of H_2O. The solid dissolved during the above addition to yield a clear solution. After neutralization with cold dilute H_2SO_4, the solution was saturated with NaCl and the oxazinedione **1a** isolated by ethyl acetate extraction. It was identical with that prepared as described above.

Registry No.—**1a,** 24314-63-1; **1b,** 51440-82-5; **1d,** 53907-40-7; **1e,** 53907-41-8; **1f,** 53907-42-9; **1g,** 53907-43-0; **4a,** 53907-44-1; **4b,** 53907-45-2; **6,** 45514-70-3; maleic anhydride, 108-31-6; trimethylsilyl azide, 4648-54-8; citraconic anhydride, 616-02-4; fluoromaleic anhydride, 2714-23-0; dichloromaleic anhydride, 1122-17-4; bromomaleic anhydride, 5926-51-2.

References and Notes

(1) This research was supported by Grant No. CA-13120-03 from the National Cancer Institute and Contract No. DAMD 17-74-C-4100 from the U.S. Army Medical Research and Development Command. This is Contribution No. 1303 to the Army Research Program on Malaria.

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(11) Although acyl azides are known to react with silylamines to generate silyl azides, e.g., $Me_3SiNHBu + PhCON_3$ + cat. $AlCl_3 \rightarrow Me_3SiN_3 +$ PhCONHBu [K. Rühlmann, A. Reiche, and M. Becker, *Chem. Ber.,* **98,** 1814 (1965)], acyloxysilanes do not react with acyl azides, e.g., $Bu-CO_2SiMe_3 + BuCON_3 \not\rightarrow (BuCO)_2O + Me_3SiN_3$ [S. S. Washburne and W. R. Peterson, Jr., *Synth. Commun.,* **2,** 227 (1972)].

(12) We are indebted to Mr. John Simolike for the mass spectra and to Mr. Charles Pohan for technical assistance in the laboratory.

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The Synthesis of 1,3-Diselenole-2-selones and -2-thiones

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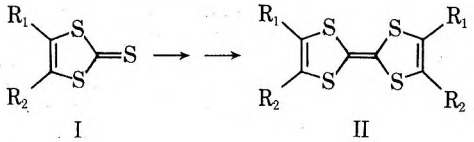
Received September 27, 1974

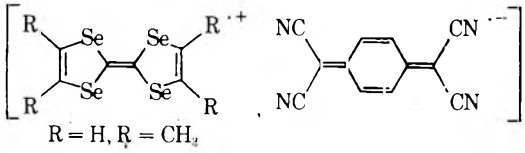
The synthesis and some physical and chemical properties of 1,3-diselenole-2-selones and -2-thiones are reported. The compounds were prepared in a three-step synthesis from *N,N*-pentamethylenediselenocarbamate and appropriate α-halo ketones.

In recent years 1,3-dithiole-2-thiones (I) have gained interest as intermediates in the synthesis of tetrathiafulvalenes (II), which have been used as the donor in several highly conducting organic "metals."[2,3]



I II

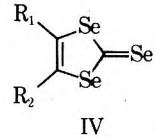
As a part of a systematic study of organic conducting solids,[4] we have been interested in substituting sulfur with selenium in order to increase electronic interactions in the donor stacks of the organic "metals." So far the selenium-containing fulvalenes have shown very promising properties in salts of the general type III.[5,6]



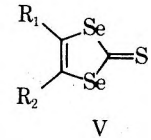
R = H, R = CH_3

III

In order to obtain the tetraselenafulvalenes in question, we have developed a general synthetic route to mono- and disubstituted 1,3-diselenole-2-selones (IV) and -2-thiones (V), which by dechalkogenizing reagents can be coupled to tetraselenafulvalenes.[5,6] Reaction sequences similar to those outlined in Scheme I have been reported for sulfur analogs of some of the compounds described in this paper.[7,8]



IV



V

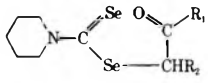
Recently Engler and Patel[5,9] have prepared 1,3-diselenole-2-selone (IV, $R_1 = R_2 = H$) from sodium acetylide, selenium, and carbon diselenide, utilizing a modified procedure originally developed to prepare 1,3-dithiole-2-thiones.[10,11] Engler and Patel also prepared several thiaselenoles.[9]

Results and Discussion

The compounds in question were all prepared by the general route outlined in Scheme I.

The first step involves nucleophilic substitution of a halogen with the *N,N*-pentamethylenediselenocarbamate anion. The substitution proceeds rapidly, but the solution was usually left 2–4 hr at room temperature to assure complete reaction. In addition to piperidinium *N,N*-pentamethylenediselenocarbamate,[12] we have used the morpholine and pyrrolidine analogs which react as well, but since piperidinium *N,N*-pentamethylenediselenocarbamate is

Table I
(2-Oxoalkyl)-*N,N*-pentamethylenediselenocarbamates

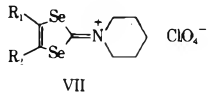


VI

Symbol	R_1	R_2	Mp, °C	Yield, %	Nmr[a] δ, ppm (rel to TMS): R_1	R_2, $-Se-\underset{\vert}{C}H-$	$-N(CH_2-)_2$	$H_2C(CH_2-)_2$
VIa	CH_3	H	45–46	83	2.40 (3 H)	4.45 (2 H) $J = 7$ Hz	3.9 and 4.45 (4 H)	1.69 (6 H)
VIb	CH_3	CH_3	43–44	79	2.31 (3 H)	1.47 (3 H), 4.94 (1 H)	4.07 (4 H)	1.69 (6 H)
VIc	Ph	H	99–102	95	7.4–8.25 (5 H)	5.06 (2 H)	3.9 and 4.45 (4 H)	1.75 (6 H)
VId	Ph	Ph		15	*b*	*b*	*b*	*b*

[a] $CDCl_3$. [b] Not recorded.

Table II
2-*N,N*-Pentamethylenimino-1,3-diselenolium Perchlorates

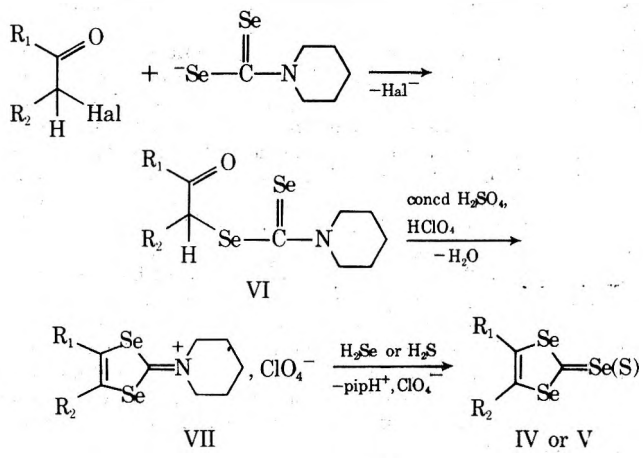


VII

Symbol	R_1	R_2	Yield, %	Nmr, δ (rel to TMS): R_1	R_2	$=N(CH_2-)_2$	$-CH_2-(CH_2)-CH_2-$
VIIa	H	CH_3	87	7.83 (1 H), 2.54 (3 H)[a] $J = 1.5$ Hz		3.97 (4 H)	1.8–2.15 (6 H)
VIIb	CH_3	CH_3	91	2.66 (6 H)[b]		3.66 (4 H)	1.7–2.1
VIIc	H	Ph	91	7.89 (1 H), 7.59 (5 H)[c]		3.90 (4 H)	1.8–2.15 (6 H)
VIId	Ph	Ph	90				

[a] $(CD_3)_2CO$. [b] CD_3CN. [c] CF_3COOH.

Scheme I



readily obtained[13] and relatively stable, it was generally preferred.

The resulting oxo esters (VI) obtained are crystalline, colorless solids, and can be recrystallized from nonpolar solvents. Results are summarized in Table I.

The ring closure of the oxo esters was found to proceed smoothly in concentrated sulfuric acid. The hydrosulfates obtained were converted to perchlorates or fluoroborates by treating the reaction mixture with excess perchloric or fluoroboric acid. Various other procedures, including treatment of the esters with acetic anhydride containing fluoroboric or perchloric acid, were tested, but all tended to give lower yields due to decomposition.

We have characterized the 2-immonio-1,3-diselenoles as their prechlorates (VII) since these salts are the ones most readily isolated. *However, an evident detonation of 1,3-dithiolylium perchlorate has recently been reported,* and although we have not so far observed any spontaneous detonation of VII it might be advisable to handle these substances with care only in small quantities.

Compounds obtained are colorless crystalline solids, but may be pink due to a small amount of free selenium, which can be removed by dissolving the salts in acetonitrile, filtering, and precipitating with ether. Results are summarized in Table II.

Cleavage of VII with excess H_2Se or H_2S was achieved in methanol or methanol–water mixtures. The slightly soluble perchlorates (VIIc and VIId) were suspended in methanol and an equimolar amount of pyridine added as a catalyst. Compounds VIIa and VIIb were treated with excess H_2Se or H_2S in 70% methanol–water without catalyst, since pyridine or $NaHCO_3$ tended to produce polymeric tars instead of the desired selones or thiones.

The 1,3-diselenole-2-selones (IVa–d) are red crystalline solids, whereas the -2-thiones (Va and b) are yellow.

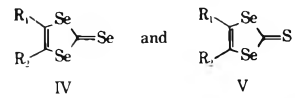
Ir spectroscopy is a convenient tool for the identification of compounds IV and V since they both exhibit a very characteristic pattern of two strong (absorption) bands in the 700–1100-cm^{-1} region which arise from the Se–CSe–Se or Se–CS–Se grouping. The high-frequency bands are found at 880–920 cm^{-1} for IV and at 920–1020 cm^{-1} for V and have been approximately ascribed to C=Se or C=S stretching vibrations, respectively.[14] The low-frequency band is found at 750–780 cm^{-1} for both compounds and is approximately described as a C—Se stretching band.[14]

Uv–Visible Spectra. 1,3-Diselenole-2-selone[5] was reported to have a maximum at 555 nm. Aliphatic substitution has only a minor effect, whereas the aryl-substituted compounds as expected exhibit a shift to higher energy (see Table III). The two analogous 2-thiones exhibit a band at approximately 450 nm.

Nmr spectral data are summarized in Table III.

Chemical Properties. Preliminary investigations of the chemical properties of IV and V have given the following

Table III
1,3-Diselenole-2-selones and -2-thiones[a]



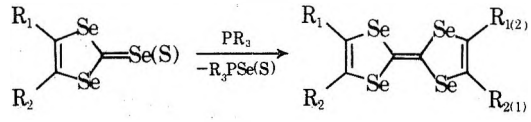
IV V

Symbol	R_1	R_2	Yield, %	Mp, °C	ir, cm^{-1} [b]	Uv-vis, nm (ε)[c]	Nmr,[e] δ, ppm
IVa	CH_3	H	66	80–81	890, 880, and 700	558 (197), 417 (15,500) 318 (870), 266 (7300)	2.42 (3 H), 7.42 (1 H), J = 1.5 Hz
IVb	CH_3	CH_3	60	149–150	890, –, and 762	555 (224), 424 (14,800) 328 (730), 266 (6200)	2.25
IVc	Ph	H	86	121–122	902, 885, and 732	524 (296), 431 (16,800)	7.36 (5 H), 7.87 (1 H)
IVd	Ph	Ph	55	161–163	902, 889, and 750	528[d] (291), 434 (19,300)	7.15
Va	CH_3	H	90	81–81.5	1020, 990, and 752	460 (sh), 382 (15,000) 295 (1400), 255 (9800)	2.42 (3 H), 7.23 (1 H), J = 1.5 Hz
Vb	CH_3	CH_3	87	101–102	1020, –, and 772	453 (53), 385 (13,800) 304 (1000), 276 (2400) 254 (8300)	2.19

[a] Satisfactory analytical data (±0.3 for C, H) were obtained for all compounds listed in the table. [b] KBr. [c] Hexane. [d] CH_2Cl_2. [e] $CDCl_3$ relative to TMS.

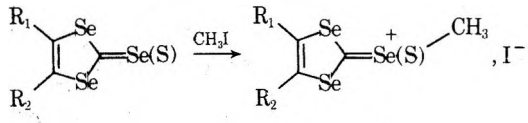
results. (1) Both selones and thiones can, in analogy with previous reports,[5,6] be coupled (by treatment with triphenylphosphine or trialkyl phosphites) to give tetraselenafulvalenes in 30–60% yield (Scheme II). (2) Treatment of IV

Scheme II



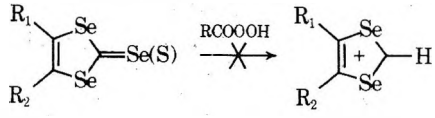
or V with excess methyl iodide gives methiodides[15] (Scheme III). (3) 1,3-Dithiolium salts can be prepared by

Scheme III



peracid oxidation of 1,3-dithiole-2-thiones.[1,16] Several attempts to prepare the hitherto unknown 1,3-diselenolium salts (VIII) by this method (Scheme IV) were unsuccessful,

Scheme IV



VIII

probably due to oxidation of the selenium atoms in the ring.[5]

Summary

The synthetic route described above provides a pathway to mono- and disubstituted 1,3-diselenole-2-selones and -2-thiones. When compared to Engler and Patel's procedures,[5,9] the advantage of the present method is that 4,5-disubstituted 1,3-diselenoles are obtainable, since no acetylenic hydrogen is required.

Experimental Section

(2-Oxoalkyl)-*N,N*-pentamethylenediselenocarbamates. VIb. Piperidinium *N,N*-pentamethylenediselenocarbamate (0.03 mol) dissolved in 60 ml of dry CH_2Cl_2 was added, under argon, to a stirred solution of 3-bromo-2-butanone (0.04 mol) in 200 ml of dry CH_2Cl_2. After the addition was completed, the solution was left with stirring at room temperature for 4 hr, and then washed with five 100-ml portions of water and dried over $MgSO_4$, and the solvent evaporated *in vacuo*. The resulting yellow oil was recrystallized from hexane to yield slightly yellow crystals of VIb. VIa was prepared in the same manner as VIb from chloroacetone. VIc and VId were prepared from phenacyl bromide and 2-bromo-1,2-diphenylethanone, respectively. Both recrystallized from cyclohexane.

2-(*N,N*-pentamethylenimino)-1,3-diselenolium Salts. VIIb. VIb (0.003 mol) was dissolved slowly in 3 g of concentrated H_2SO_4. After standing 0.5 hr at room temperature enough EtOAc was added cautiously to cause starting precipitation of the hydrosulfate. The solution was then filtered into a mixture of 1–2 ml of 70% $HClO_4$ and 50 ml of absolute EtOH, and 300–500 ml of ether was added. The resulting white solid was filtered off, washed with ether, and dried *in vacuo*. VIIa, VIIc, and VIId were prepared in the same manner as VIIb.

1,3-Diselenole-2-selones or -2-thiones. IVb. VIIb (0.0025 mol) was dissolved in 60 ml of 70% MeOH–water cooled to −10°, and the stirred solution, which was kept under argon, treated with a sixfold excess of H_2Se.[17] A red solid was slowly formed and the solution was allowed to warm to 0° over 2–3 hr. Water (40 ml) was added and the solid filtered off and dried in a desiccator over P_2O_5. Recrystallization from heptane yielded bright red plates of IVb. IVa was prepared in the same manner as IVb.

IVc and IVd. Since VIIc and VIId are rather insoluble, they were suspended in absolute MeOH, and an equimolar amount of pyridine was added as a catalyst. Both products were recrystallized from absolute EtOH. Va and Vb were prepared by essentially the same procedure as IVb. Due to its lower reactivity, however, H_2S was passed through the stirred solution at room temperature for 4–6 hr.

Acknowledgment. The present work was supported by Materials Science Office, Advanced Research Projects Agency, Department of Defense. K.B. wishes to thank Statens Naturvidenskabelige Forskningsraad for a travel grant.

Registry No.—IVa, 53808-61-0; IVb, 53808-62-1; IVc, 53808-63-2; IVd, 53808-64-3; Va, 53808-65-4; Vb, 53808-66-5; VIa, 53808-67-6; VIb, 53808-68-7; VIc, 53808-69-8; VId, 53808-70-1; VIIa, 53808-72-3; VIIb, 53808-74-5; VIIc, 53808-76-7; VIId, 53808-78-9; piperidinium *N,N*-pentamethylenediselenocarbamate, 30611-91-7; 3-bromo-2-butanone, 814-75-5; chloroacetone, 78-95-5; phenacyl bromide, 70-11-1; 2-bromo-1,2-diphenylethanone, 1484-50-0.

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Conformational Analysis of the Favorskii Rearrangement Using 3(a)-Chloro-3(e)-phenyl-*trans*-2-decalone and 3(e)-Chloro-3(a)-phenyl-*trans*-2-decalone[1a]

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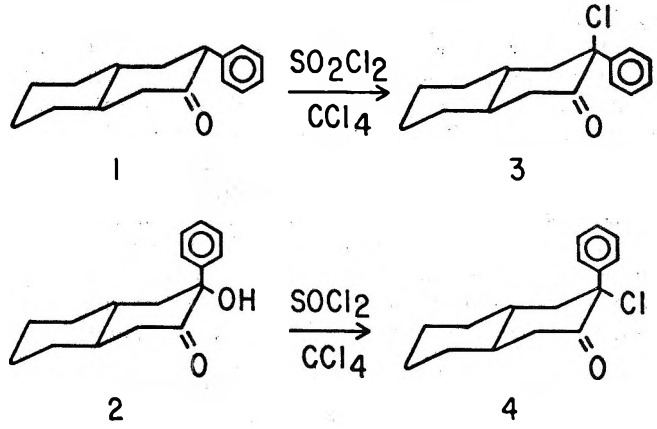
Received July 26, 1974

The starting material for the synthesis of the isomeric chloro ketones (3 and 4) was *trans*-2-decalone, which was converted to 3(e)-phenyl-*trans*-2-decalone (1) and 3(e)-hydroxy-3(a)-phenyl-*trans*-2-decalone (2). Compound 1 was chlorinated by sulfuryl chloride in carbon tetrachloride to yield the axial chloro ketone 3, while compound 2 was chlorinated by thionyl chloride in carbon tetrachloride to yield the equatorial chloro ketone 4. Potassium *tert*-butoxide was used to effect the rearrangement both in ethanol (E) and 1,2-dimethoxyethane (D). The product from 3 when the rearrangement was performed in D included 2-phenylhexahydroindan-2-carboxylic acid [isolated as the methyl ester (5)] and 2-phenacyl-1-cyclohexaneacetic acid [isolated as the methyl ester (6)]. Rearrangement of 3 in E yielded 5, 6, and 1-ethoxy-3-phenyl-*trans*-2-decalone (7). Favorskii products were not evident when 4 was subjected to rearrangement conditions. It can be concluded that the axial conformation of the chlorine atom is more favorable for the Favorskii rearrangement. Compound 7 was apparently produced either from a cyclopropanone intermediate or an enol allylic chloride.

An attempt was made by Smissman et al.[2] to determine whether a cyclopropanone intermediate or a dipolar ion was operative in the Favorskii rearrangement of a pair of conformers, viz., 3(a)-bromo-*trans*-2-decalone (8) and 3(e)-bromo-*trans*-2-decalone (9). Since the axial compound gave no rearrangement product in either polar or nonpolar solvents whereas the equatorial compound rearranged in both solvent types, it was concluded that the results of this study disputed the role of the dipolar ion as an active participant in the Favorskii rearrangement. If this conclusion were valid, if not on a general basis, then at least for rigid systems such as the *trans*-decalones, it could be predicted that of the two conformers used in the present study, viz., 3(a)-chloro-3(e)-phenyl-*trans*-2-decalone and 3(e)-chloro-3(a)-phenyl-*trans*-2-decalone, the equatorial isomer would give the Favorskii product.

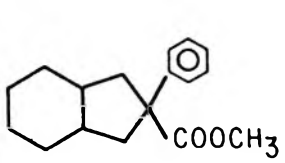
Results

The two chloro ketones 3 and 4 were synthesized by the chlorination of 3(e)-phenyl-*trans*-2-decalone (1) and 3(e)-hydroxy-3(a)-phenyl-*trans*-2-decalone (2). Compounds 1 and 2 were synthesized by published methods.[3] Potassium *tert*-butoxide was used to effect the rearrangement both in the polar solvent ethanol and in the nonpolar solvent 1,2-dimethoxyethane. The products of the rearrangement were hydrolyzed and separated into an acidic fraction and a neutral fraction. The former was subjected to Fischer–Spier esterification prior to column chromatography on alumina. The components of the neutral fraction were separated by column chromatography on silica gel.



Rearrangement of the axial chloro ketone 3 in ethanol gave, after esterification, the methyl ester of 2-phenylhexahydroindan-2-carboxylic acid (5, 2% yield) and 2-phenacyl-1-cyclohexaneacetic acid (6, 2% yield). The neutral components included compounds 1-ethoxy-3-phenyl-*trans*-2-decalone (7, 2% yield) and 3(e)-hydroxy-3(a)-phenyl-*trans*-2-decalone (2, 42% yield). A polymeric material was also isolated.

The yield of 5 was similar (2%) when the rearrangement of 3 was performed in dimethoxyethane. Compound 6 was also isolated (<1% yield). Sublimation of the crude acid fraction prior to Fischer–Spier esterification yielded benzoic acid. The neutral components included polymeric material.



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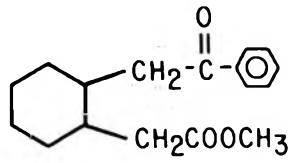

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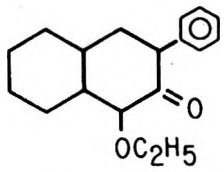


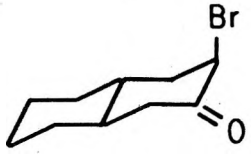
7

Base treatment of the equatorial chloro isomer **4** when dissolved in ethanol yielded the ester **6** (7% yield) and some unknown material. The neutral products contained polymeric material.

Acidic products from the rearrangement of **4** in a nonpolar solvent included benzoic acid. Compound **6** was isolated after esterification (<1% yield). Again polymeric material was present in the neutral fraction.

Discussion

Previous results[2] using the bromo compounds **8** and **9** had indicated that the dipolar ion is not a necessary inter-



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9

mediate in the Favorskii rearrangement. It was suggested by Bordwell[4a] and House[4b] that the axial bromo compound **8** undergoes side reactions faster that it undergoes the Favorskii rearrangement. To provide further evidence concerning the steric requirements of the Favorskii rearrangement, compounds **3** and **4** were synthesized. The infrared analysis of these compounds supported the assigned stereochemistry, since the carbonyl stretching frequency observed in **4** was increased by about 20 cm^{-1} relative to **3**.[5] Only the axial isomer **3** gave the Favorskii compound **5** and the neutral compound **7** even though larger amounts of **4** were used in the study. Both isomers gave compound **6** and both produced polymeric compounds as the major products.

Many references to the Favorskii rearrangement may be found in the papers by Bordwell, who has provided additional evidence that ionization of the carbon–halogen bond facilitates the formation of the Favorskii product, and that a dipolar ion is probably in equilibrium with a cyclopropanone[6-8] (Figure 1).

The results obtained from this study of **3** and **4** indicate that the conformation of the chlorine atom does influence the yield of compound **5**. That **7** could have arisen from 1-chloro-3-phenyl-*trans*-2-decalone, which might have been present as an impurity in compound **3**, was discounted. Analysis by NMR did not reveal the presence of such an impurity, and yet compound **7** could be obtained in enhanced yield (10–15%) when **3** was treated with sodium ethoxide in ethanol. Further, there was no difference in the physical properties of **3** when it was prepared from **1** or from **13**. A cyclopropanone intermediate might be involved

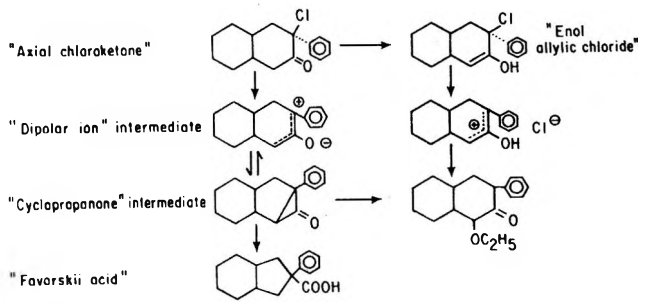
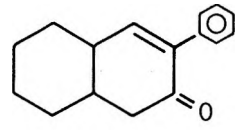


Figure 1. Intermediates involved in the formation of the Favorskii acid **5** and compound **7**.



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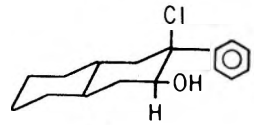

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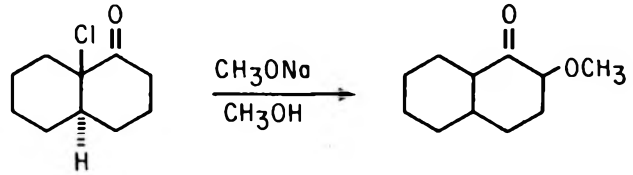
in the formation of **7**. A similar explanation was advanced by House and Frank,[9] who demonstrated that the *trans*-decalone derivative **14** under Favorskii rearrangement conditions will produce side product **15**, analogous to com-

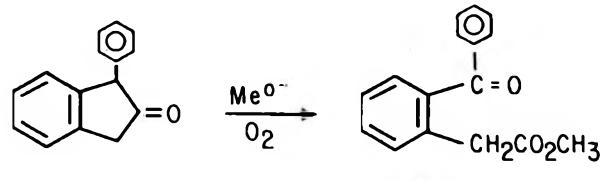


14 15

pound **7**. Alternatively, as envisioned by Bordwell and Carlson,[7] the enolate anion may form an equilibrium with an enol allylic chloride and its corresponding ion pair. The latter could then react with ethanol to produce compound **7**.

It is unlikely that hydroxy ketone **2** was produced by an SN1 type reaction during the course of the reaction, since it was demonstrated that hydroxy ketone formation during the course of the Favorskii reaction is not subject to a salt effect.[4a] Therefore, compound **2** probably arose from the corresponding alkoxy oxirane during work-up.

Compound **6** was produced by ring opening but the reaction mechanism was not elucidated. A similar acidic product was observed when the bromo compounds **8** and **9** were exposed to Favorskii conditions.[2] Bordwell[10] has demonstrated that compound **10** is converted to compound **11** by reaction with oxygen in the presence of methanolic sodium hydroxide, which suggests that compound **6** is formed by a similar mechanism. Apparently, the benzoic acid found in the present investigation was generated from acid **6**. The



10 11

formation of polymers under Favorskii conditions might be a consequence of alkylation by the enolate anion,[11] although the possibility that an enone such as **12** might be produced and then polymerize should be considered.

If we invoke a dipolar ion intermediate, then the sequence of events illustrated in Figure 1 will explain why it was the axial chloro and not the equatorial isomer that gave the desired Favorskii acid. However, the results obtained in this study are in contrast to those obtained by Smissman et al.[2] in the closely related system described above. Presumably, the axial bromo ketone **8** and the equatorial chloro ketone **4** undergo side reactions faster than they can undergo the Favorskii rearrangement.

Although an interesting example of a Favorskii-like reaction has been reported where an internal SN2 displacement of the halide ion probably occurs,[12] it appears that in the Favorskii rearrangement of α-halo ketones such a displacement is unlikely.

Experimental Section

3(a)-Chloro-3(e)-phenyl-*trans*-2-decalone (3). A. Sulfuryl chloride (650 mg) was added to a solution of 3(e)-phenyl-*trans*-2-decalone (1.1 g) in CCl_4 (25 ml). After 6 hr at room temperature, the mixture was poured onto ice water. The CCl_4 layer was separated, dried ($MgSO_4$), and evaporated to yield a solid, mp 115° (recrystallized from acetone in 72% yield). Anal. Calcd for $C_{16}H_{19}ClO$: C, 73.10; H, 7.25; Cl, 13.5. Found: C, 73.23; H, 7.40; Cl, 13.20. Infrared ($CHCl_3$) 3.43, 3.5, 5.85, 6.26, 6.92 μ.

B. A solution of 2(e)-phenyl-*trans*-decalin 2,3-oxide[3] (300 mg) in $CHCl_3$ (30 ml) was stirred with concentrated HCl (5 ml) for 45 min. The $CHCl_3$ layer was separated, dried, and evaporated to yield an oil, 3(a)-chloro-3(e)-phenyl-*trans*-2-decalol (**13**): trifluoroacetate derivative mp 65–66° (recrystallized from isopropyl alcohol). Anal. Calcd for $C_{18}H_{20}ClF_3O_2$: C, 60.84; H, 5.53; Cl, 9.8. Found: C, 60.84; H, 5.53; Cl, 9.8. Compound **13** (250 mg) was dissolved in a solution of DMSO (4 ml) and acetic anhydride (4 ml)[13] and the mixture was then stirred for 24 hr at room temperature. Addition of water precipitated an oil which then crystallized, mp 115° (acetone).

3(e)-Chloro-3(a)-phenyl-*trans*-2-decalone (4). Thionyl chloride (12 ml) was added to a solution of 3(e)-hydroxy-3(a)-phenyl-*trans*-2-decalone (2 g) in CCl_4 (4 ml). The solution was stirred for 18 hrs and then ice-cold water was added dropwise until the thionyl chloride was destroyed. The CCl_4 layer was separated, dried over $MgSO_4$, and evaporated to yield an initial oily product which was recrystallized from Skelly B (mp 136–137°) in 55% yield. Anal. Calcd for $C_{16}H_{19}ClO$: C, 73.10; H, 7.25; Cl, 13.5. Found: C, 73.14; H, 7.39; Cl, 13.32. Infrared ($CHCl_3$) 3.42, 3.5, 5.78, 6.22, 6.89 μ.

Favorskii Rearrangement of Compounds 3 and 4. To study the reaction under polar conditions a solution of compound **3** (1.6 g) and potassium *tert*-butoxide (2 g) or **4** (3.7 g) and potassium *tert*-butoxide (4.6 g) in absolute ethanol (125 ml) was stirred at room temperature for 10 hr. Reactions using nonpolar conditions involved stirring a solution of compound **3** (7.8 g) and potassium *tert*-butoxide (9.6 g) or compound **4** (11.3 g) and potassium *tert*-butoxide (12.8 g) in dimethoxyethane (250 ml). The solvent was then removed by evaporation and water (30–100 ml) was added. The mixture was refluxed for 8 hr, cooled, and extracted with ether (4 × 15 ml or 4 × 50 ml) to remove neutral fraction A. Acidification of the mother liquor with 10% HCl, followed by extraction with ether (4 × 15 ml or 4 × 50 ml), gave an acidic fraction B.

Analysis of Fractions A and B Obtained from 3 Using Potassium *tert*-Butoxide in Ethanol. Fraction B was dissolved in methanol which had been saturated with dry HCl gas, and te solution was then refluxed for 24 hr. Dry column chromatography using $CHCl_3$ and neutral alumina resulted in the isolation of the Favorskii methyl ester **5** (33 mg): 2.2% yield; ir (liquid film) 5.78 (s), 6.24, 6.9 μ; NMR ($CDCl_3$) δ 7.2 (5 H, aromatic), 3.62 (3 H, methyl ester), 0.8–3.1 (14 H, aliphatic envelope). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.02; H, 8.50. Found: C, 79.48; H, 7.60.

A sample of the Favorskii methyl ester **5** was refluxed with 20% KOH (aqueous) solution for 6 hr. Upon cooling the solution was extracted with ether. The aqueous phase was separated, acidified with 10% HCl, and extracted with ether. The ether solution was separated, washed with water, dried, and evaporated to yield an oil which crystallized (mp 111–112° from aqueous ethanol): ir (liquid film) 2.7–4.2, 5.85, 6.24 μ; NMR ($CDCl_3$) δ 10.87 (1 H, broad acidic), 7.3 (5 H, aromatic), 0.2–2.8 (14 H, aliphatic envelope). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.6; H, 8.25. Found: C, 78.94; H, 8.71.

The second component of the acidic fraction was the methyl ester **6** (28 mg, 1.7% yield): ir (liquid film) 5.76, 5.92, 6.25, and 6.9 μ; NMR ($CDCl_3$) δ 7.9 (aromatic ortho protons), 7.3 (aromatic meta protons), 3.6 (3 H, methyl ester), 0.7–3.1 (14 H, aliphatic). The ester was converted to its 2,4-dinitrophenylhydrazone derivative, mp 165° (from aqueous ethanol). Anal. Calcd for $C_{23}H_{26}N_4O_6$: C, 60.51; H, 6.18. Found: C, 60.64; H, 5.79. A 2,4-DNP derivative (mp 126–129°) was also prepared of the free acid of **6**. Anal. Calcd for $C_{22}H_{24}N_4O_6$: N, 12.7. Found: N, 12.6.

Ether extract A was chromatographed on a silica gel column using $CHCl_3$–CCl_4 (1:1) as the eluent. The first fractions contained **7** (24 mg, 1.4%): mp 63° (isopropyl alcohol–water). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.4; H, 8.8. Found: C, 79.63; H, 9.1. NMR ($CDCl_3$) δ 7.2 (5 H, aromatic), 4.25 (1 H, methine), 3.5 (3 H, methine and methylene superimposed), 0.5–2.5 (aliphatic envelope). Successive fractions contained the hydroxy ketone **2** in 42% yield (379 mg) and finally an unknown polymeric material (240 mg).

Analysis of Fractions A and B Obtained from 3 Using Potassium *tert*-Butoxide in 1,2-Dimethoxyethane. Benzoic acid was sublimed by heating fraction B in a sublimation flask at 120° (oil bath). Identification was achieved by mixture melting point, ir, and NMR analysis.

Fraction B was subjected to Fischer–Spier esterification. The methanolic solution was separated from an insoluble material (2.1 g) and then evaporated to yield an oil (750 mg) which was then chromatographed on neutral alumina (dry column) by eluting with chloroform. The first fraction contained the methyl ester **5** (193 mg, 2.6%) whereas the second fraction contained the methyl ester **6** (27 mg), <1% yield.

Ether extract A after evaporation left a polymeric residue (mp 215–220°, mol wt 660).

Analysis of Fractions A and B Obtained from 4 Using Potassium *tert*-Butoxide in Ethanol. Ether extract B was evaporated and esterified (methanolic HCl). After removal of the solvent an oil was obtained which was purified by dry column chromatography (alumina and $CHCl_3$). The first fraction was an unknown (18 mg), ir 5.76 μ, NMR ($CDCl_3$) δ 7.3, 3.65, 3.55, 0.8–3.05, whereas the major fraction was the methyl ester **6** (260 mg, 7% yield).

Analysis of ether extract A by column chromatography (silica gel and $CHCl_3$–CCl_4) revealed the presence of an unknown polymeric material.

Analysis of Fractions A and B Obtained from 4 Using Potassium *tert*-Butoxide in Dimethoxyethane. After evaporation of the ether, the acidic fraction B was heated at 120° in a sublimation apparatus. Benzoic acid was sublimed. A Fischer–Spier esterification was then performed on the residue. The esterified products were chromatographed on alumina (Woelm), eluting with chloroform. The first fraction (50 mg) was not identified. Its infrared spectrum was devoid of aromatic and carbonyl absorption bands. A second fraction was also unknown (176 mg). The third fraction was identified as the methyl ester of **6** (38 mg, 1% yield).

Analysis of the residue obtained from ether extract A by column chromatography (silica gel and $CHCl_3$–CCl_4) revealed the presence of an unknown polymeric material.

Registry No.—**1**, 19297-03-1; **2**, 33201-01-3; **3**, 53993-55-8; **4**, 53993-56-9; **5**, 53993-57-0; **5** free acid, 53993-58-1; **6**, 53993-59-2; **6** 2,4-DNP, 53993-60-5; **6** free acid 2,4-DNP, 53993-61-6; **7**, 53993-62-7; **13**, 53993-63-8; **13** trifluoroacetate, 53993-64-9; 2(e)-phenyl-*trans*-decalin 2,3-oxide, 54053-46-2.

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(1) (a) Presented before the 9th Middle Atlantic Regional American Chemical Society Meeting, Wilkes Barre, Pa., April 23–26, 1974. (b) Address correspondence to this author at Merck Institute for Therapeutic Research, West Point, Pa. 19486. (c) Deceased.

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Stereochemistry in Trivalent Nitrogen Compounds. XXV. Solvent and Medium Effects on Degenerate Racemization in Aminosulfenyl Chlorides[1]

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Received August 12, 1974

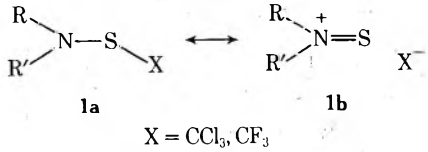
The barriers to degenerate racemization in a series of *N*-benzyl-*N*-methylsulfenamides, $RSN(CH_3)CH_2C_6H_5$, have been determined by observing the coalescence of the nmr signals of diastereotopic benzyl methylene protons which is associated with degenerate racemization. In each of these compounds the ligand, R, at sulfur has a heteroatom (Cl, O, N, or S) attached to sulfenyl sulfur. The barrier of the chlorosulfenamide (R = Cl) in contrast to the other members of the series, showed a dramatic decrease (4.2 kcal/mol) when the solvent was changed from toluene-d_8 to chloroform-*d*. Addition of tetramethylammonium chloride or tetraethylammonium perchlorate also results in a substantial increase in the rate of degenerate racemization. These changes provide evidence for a pathway for degenerate racemization in addition to torsion about the N–S bond. Heterolysis of the S–N bond and SN2 displacement by chloride ion at sulfur were considered as possible racemization mechanisms.

The substantial barriers to rotation about the N–S formal single bond in sulfenamides renders this moiety a unit of axial chirality in suitably substituted compounds.[3] This axial chirality can be made manifest by the observation of chemical shift nonequivalence of diastereotopic benzyl methylene protons in the low-temperature nmr spectra of *N*-benzylsulfenamides. The coalescence of signals for diastereotopic benzyl methylene protons which is observed at higher temperatures is associated with a topomerization in which a chiral sulfenamide molecule is reversibly interconverted with its mirror image, *i.e.*, a degenerate racemization.

It has been shown that the electronic nature of the substituent at the sulfenyl sulfur atom has a major effect on the chemical properties of the sulfenamide group.[4] Similarly the conformational properties of sulfenamides are strongly related to the electron-withdrawing power of the ligand at sulfenyl sulfur. Electron-withdrawing substituents in the para position of benzenesulfenamides dramatically increase the barrier to torsion about the nitrogen–sulfur bond.[5] Thus, the barrier to rotation about the N–S bond in *N*-benzenesulfonyl-*N*-isopropyl-2,4-dinitrobenzenesulfenamide is nearly 4 kcal/mol higher than that in the corresponding benzenesulfenamide. The rate data obtained for a series of para-substituted *N*-benzenesulfonyl-*N*-isopropylbenzenesulfenamides afforded a Hammett reaction constant (ρ) of −2.1 for torsion about the sulfenyl S–N bond as a function of the para substituent on the sulfenyl phenyl ring. Analysis of the linear free energy relationships for compounds in this and related series implicated p–d π bonding between nitrogen and sulfur as a major contributor to the enhanced barriers in these compounds.[5]

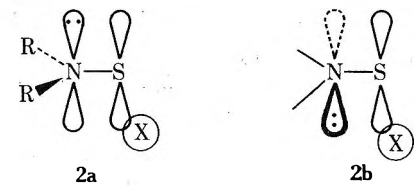
By contrast, differences in p–d π bonding did not seem to have an appreciable effect on the nitrogen inversion barriers in *N*-(arenesulfenyl)aziridines.[6] The dependence of the nitrogen inversion barriers upon the electron-withdrawing capability of the para substituent in the sulfenyl phenyl ring was negligible and the Hammett constant obtained, −0.16 ± 0.1, was not significantly outside of experimental error. On the other hand, the presence of a trihalomethyl group at sulfenyl sulfur results in a fairly substantial lowering of the nitrogen inversion barrier. The inversion barriers in 1-trichloromethanesulfenyl and 1-trifluoromethanesulfenyl-2,2-dimethylaziridine are 2–2.5 kcal/mol less than the barriers which would be estimated on the basis of steric factors alone.[7] This rate acceleration was attributed to σ–π conjugation (negative hyperconjugation) as expressed in canonical structures **1a** and **1b.** A similiar explanation had been used by Bystrov and coworkers to account for the anomalously low nitrogen inversion barriers in methylenealkoxyaziridines.[8] They referred to overlap between the nitrogen lone-pair orbital and C–O antibonding σ^* orbital. This explanation in a molecular orbital framework is equivalent to that expressed in a resonance framework using canonical structures **1a** and **1b.** The observed dependence of the nitrogen inversion barriers in sulfenylaziridines upon the electronic nature of substituents at sulfenyl sulfur also implies that the nearly planar geometry at nitrogen found in the solid state for an *N*-trichloromethanesulfenylsulfonamide derives from σ–π conjugation rather than p–d π bonding as originally suggested.[3c]

Since σ–π conjugation has been implicated as the origin for reduced nitrogen inversion barriers in sulfenylaziridines as well as decreased ground-state pyramidality in an acyclic sulfenylsulfonamide, it might also play a role in determining the magnitude of S–N torsional barriers in acyclic sulfenamides. Thus, overlap between the nitrogen lone-pair orbital and the sulfur atomic orbital used in bonding to X can be important only in the ground state **2a** where the



1a **1b**

X = CCl_3, CF_3



2a **2b**

XSN plane bisects the RNR′ angle and must be negligible in the transition state for torsion where the S–X bond axis lies in or near the nodal surface of the nitrogen lone-pair orbital. The effect of significant σ–π conjugation in the ground state would be to increase the torsional barrier

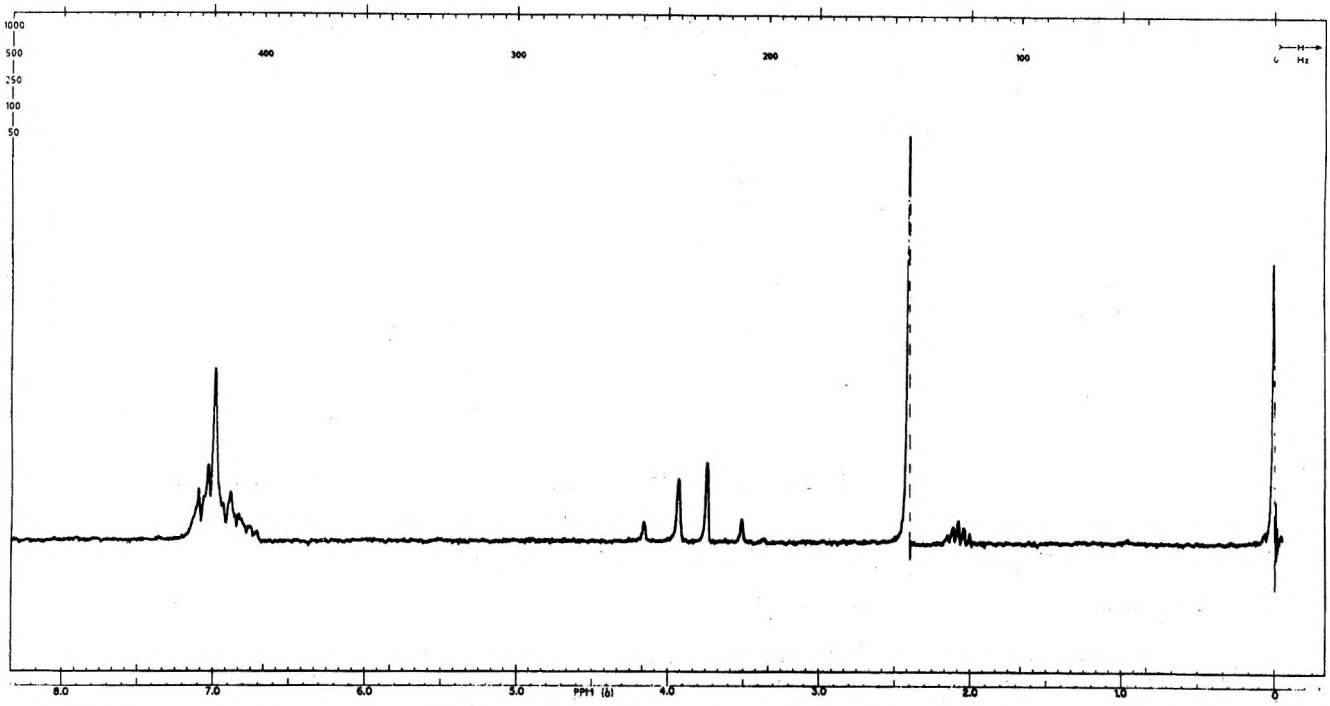
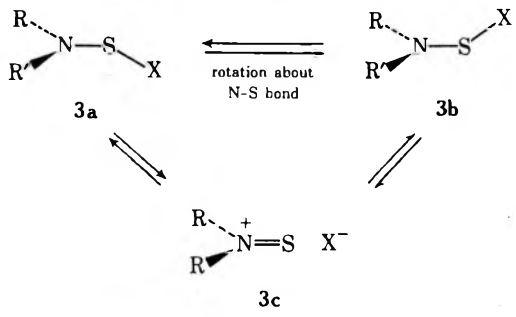


Figure 1. Low-temperature nmr spectrum of *N*-benzyl-*N*-methylaminosulfenyl chloride, **6a**, in toluene-d_8.

when the substituent at sulfenyl sulfur has a strong inductive (electron withdrawal) capability. Indeed, the substantial barriers to degenerate racemization in trichloromethanesulfenamides[3] can most probably be attributed, at least in part, to σ–π conjugation. On the other hand, evidence based upon linear free energy relationships rules out this explanation for the equally high barriers in 2,4-dinitrobenzenesulfenamides.

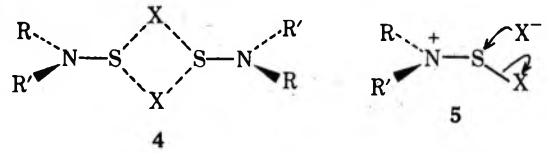
In addition, canonical structure **1b** suggests a possible mechanism for degenerate racemization which might compete with torsion about the N–S bond (Scheme I). Thus, heterolysis of the S–X bond might lead to ion pair **3c** in which the nitrogen–sulfur double bond is prochiral and has enantiotopic faces. Capture of the anion X^- at either of the two enantiotopic faces would produce the corresponding enantiomer **3a** or **3b**. Thus, ion pair **3c** is a possible intermediate in the reversible interconversion of **3a** and **3b**.

Scheme I
Mechanistic Possibilities for Degenerate Racemization in Sulfenamides



3a **3b** **3c**

Jackson, *et al.*,[9] have considered a third possible mechanism for degenerate racemization of halosulfenamides in polar solvents, *viz.*, bimolecular halogen exchange. Since bimolecular exchange involving a transition state resembling **4** would involve inversion of configuration at sulfur, it represents a process which occurs with racemization. If exogenous chloride ion were present, SN2 displacement, **5**, might also provide a racemization mechanism.

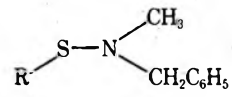


4 **5**

This paper describes a series of experiments undertaken to explore these possibilities.

Results and Discussion

Reaction of benzylmethylamine with sulfur monochloride affords either the chlorosulfenamide **6a** or the disulfenamide **6c** depending on the stoichiometry of the reaction.[4b] Thus, reaction between sulfur monochloride and 2 equiv of amine affords **6a**, while **6c** results from reaction with 4 equiv of amine. The aminosulfenyl chloride serves as a useful synthetic intermediate and reaction with sodium isopropoxide yields the isopropoxysulfenamide **6b**. The disulfenamide **6d** was obtained by reaction of 4 equiv of amine with a mixture of sulfur chlorides rich in S_3Cl_2.



6a, R = Cl
b, R = $OCH(CH_3)_2$
c, R = $N(CH_3)CH_2C_6H_5$
d, R = $SSN(CH_3)CH_2C_6H_5$

The low-temperature nmr spectra of sulfenamides **6** all exhibit chemical shift nonequivalence (AB quartet) of diastereotopic benzyl methylene protons in deuteriochloroform or deuterated toluene (Figure 1). The two isopropyl methyl groups in the isopropoxysulfenamide **6b** are also diastereotropic and appear as two overlaping doublets (Figure 2). The chemical shift nonequivalence is the result of the molecular chirality in sulfenamides **4** which results from slow rotation about sulfenyl S–N bonds[10] At higher temperatures the signals from diastereotopic groups coalesce as degenerate racemization becomes rapid on the nmr time scale and their averaged environments become enantiomeric. Free energies of activation at the coalescence

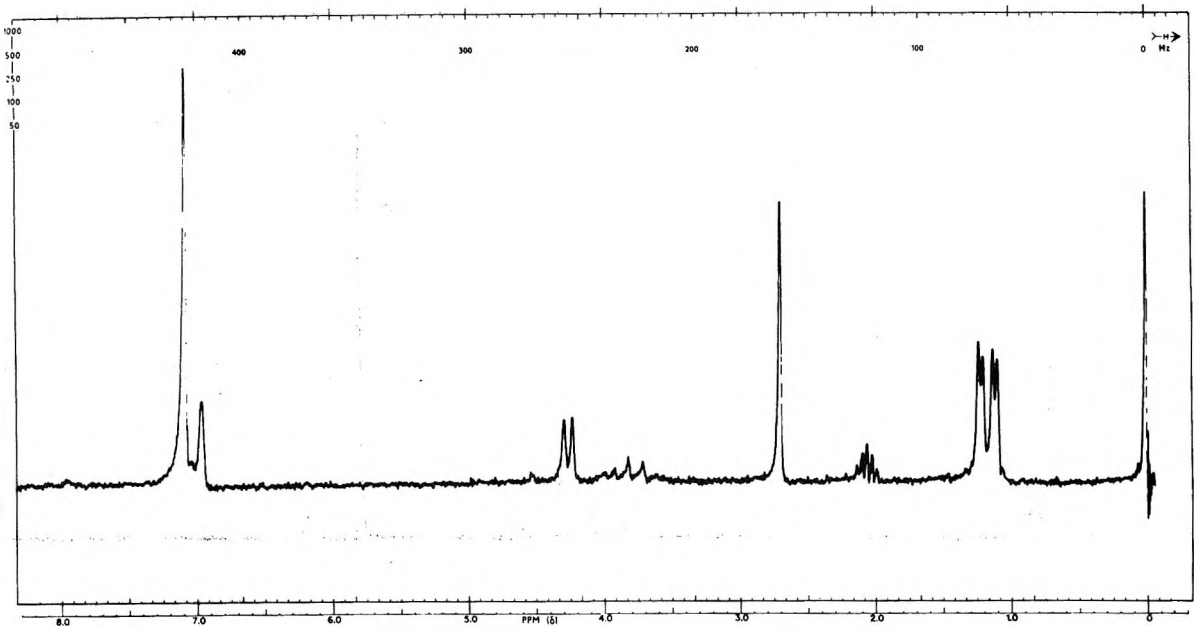


Figure 2. Low-temperature spectrum of *N*-benzyl-*N*-methylisopropoxysulfenamide, **6b**, in toluene-d_8.

points were obtained using the expression[11] $\Delta\nu = 2.22 \times (\Delta\nu^2 + 6J^2)^{1/2}$ and the the Eyring equation (Table I).

Sulfenamides which bear an additional heteroatom (Cl, O, N, or S) bonded to the sulfenyl sulfur atoms exhibit barriers which correlate qualitatively with the Pauling–Allred electronegativities of the heteroatoms.[12,13] Although the relationship for sulfenamides **6** is not monotonic, those which bear the highly electronegative atoms oxygen, **6b**, and chlorine, **6a**, have considerably higher barriers than the sulfenamides **6c** and **6d** which have the less electronegative atoms, nitrogen and sulfur, attached to sulfenyl sulfur. We have attributed these enhanced barriers to a combination of p–d π bonding and σ–π conjugation.[12]

The barriers for degenerate racemization in most sulfenamides are relatively insensitive to the nature of the solvent.[3a] This is true for the sulfenamides **6b, 6c,** and **6d.** Here, the barriers in chloroform-*d* and toluene-d_8 differ by no more than 0.6 kcal/mol, an amount which we do not regard as highly significant. Such is not the case for the chlorosulfenamide **6a.** The coalescence point and associated free energy of activation are substantially reduced (by 4.2 kcal/mol) when the solvent is changed from toluene-d_8 to chloroform-*d*. This solvent effect cannot be attributed to enhanced ground-state stabilization by p–d π bonding or σ–π conjugation. Since either should be increased in polar solvents, additional ground-state stabilization is expected to result in higher barriers in polar solvents. This solvent effect suggests that degenerate racemization of aminosulfenyl chlorides in polar solvents might take place *via* a different mechanism than that for other sulfenamides, *i.e.*, other than torsion about the nitrogen–sulfur bond.

The possible intervention of a bimolecular mechanism can be tested by examination of the effect of changed sulfenamide concentration on the coalescence temperature and calculated free energy of activation. If a bimolecular mechanism were an important pathway, the coalescence temperature would decline with increased substrate concentration and calculation of the free energy of activation, assuming first-order kinetics, would likewise result in smaller values as the concentration is increased. However, this was not observed. Change of concentration of **6a** in either toluene or chloroform from 10 to 23% w/v resulted in no change in the calculated free energy of activation. This result not only rules out bimolecular exchange but also indicates that dissocation of **6a** to form catalytic amounts of chloride anion which causes rapid stereomutation *via* SN2 displacement is not an important pathway in the absence of added chloride anion.

Addition of tetramethylammonium chloride to solutions of **6a** does appear to have a significant effect on the barrier. Barrier decreases of 1.6 and 0.9 kcal/mol were observed in deuteriochloroform and deuterated toluene, respectively. This might be due either to the intervention of SN2 displacement at sulfur or to a generalized salt effect or a combination of both. Such a generalized salt effect might be expected if heterolysis of the sulfur–chlorine bond to give in-

Table I

Compd	Hetero-atom	Solvent	Addend	$\Delta\nu$, Hz	J_{AB}, Hz	T_C, °C	ΔG^*, kcal/mol (kJ/mol)
6a	Cl	Toluene-d_8		20.8	13.8	39	15.5
6a	Cl	Chloroform-*d*		11.9	13.5	−43	11.3
6a	Cl	Toluene-d_8	Tetramethylammonium chloride (1×10^{-5} *M*)	21	14.0	22	14.6
6a	Cl	Chloroform-*d*	Tetramethylammonium chloride (4.6×10^{-5} *M*)	12	13.5	−72	10.0
6a	Cl	Chloroform-*d*	Tetraethylammonium perchloride (7×10^{-5} *M*)	12	13.5	−58	10.8
6b	O	Toluene-d_8		11.9	14.2	15	14.3
6b	O	Chloroform-*d*		10.4	14.2	12	14.2
6c	N	Toluene-d_8		44.2	14.5	−55	10.7
6c	N	Chloroform-*d*		16.5	14.5	−67	10.3
6d	S	Toluene-d_8		44.6	13.0	−46	11.2
6d	S	Chloroform-*d*		28.0	13.0	−56	10.8

termediate **3c** were the rate-determining step in the degenerate racemization. The observation that addition of tetraethylammonium perchlorate also lowers the barrier indicates that there is a salt effect and supports the existence of a mechanism for degenerate racemization involving heterolysis to give ion pair **3c**. Since the effect of tetramethylammonium chloride seems to be greater than that of tetraethylammonium perchlorate, it may well be that an SN2 mechanism becomes important when the concentration of chloride anion becomes high.

Experimental Section

Experimental Analyses were performed by Midwest Microlab, Inc. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were measured on a Varian A-60 spectrometer equipped with a Varian A-6040 variable-temperature controller. Spectra were measured on *ca.* 10% w/v solutions, except as indicated, and are referred to tetramethylsilane as internal standard. Temperatures were determined using methanol chemical shifts as described in the Varian users' manual.

***N*-Benzyl-*N*-methylaminosulfenyl Chloride, 6a.** Commercial sulfur dichloride (SCl_2) was purified by treatment with chlorine gas (to convert any sulfur monochloride present to the dichloride), followed by distillation at 30° (360 Torr), and was stored over a small amount of PCl_5. Purified SCl_2 (11.0 g, 0.1 mol) was added dropwise to a stirred, cooled (−78°) solution of benzylmethylamine (24.2 g, 0.2 mol) in petroleum ether and allowed to react for 1 hr. The reaction mixture was filtered and the solvent removed under vacuum. The residue, a yellow-orange oil, was redissolved in a minimum amount of carbon tetrachloride and treated with dry hexane to precipitate any remaining benzylmethylamine hydrochloride. The hexane–carbon tetrachloride solution was filtered and the solvent removed under vacuum (80% yield). The nmr spectra of the oily residue indicated that it was of sufficient purity: nmr ($CDCl_3$) δ 3.03 (s, CH_3), 4.38 (s, $CH_2C_6H_5$), 7.33 (s, $CH_2C_6H_5$).

***N*-Benzyl-*N*-methylisopropoxysulfenamide, 6b.** A solution of isopropyl alcohol (1 g, 0.017 mol) in cooled (0°), dry tetrahydrofuran was treated with sodium hydride (57% dispersion in oil) (0.7 g, 0.017 mol) and stirred for 1.5 hr. A solution of the chlorosulfenamide **6a** (3.2 g, 0.017 mol) in dry tetrahydrofuran was added dropwise to the solution of sodium isopropoxide and allowed to react at room temperature for 3 hr. The tetrahydrofuran was removed *in vacuo* and replaced with ether. The solution was washed with water, 10% aqueous $NaHCO_3$, and saturated aqueous NaCl and dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The residue was distilled under reduced pressure and the fraction distilling at 60–61° (0.02 mm) was collected (51% yield): nmr ($CDCl_3$) δ 2.05 (d, J = 6.2 Hz, $CH(CH_3)_2$), 2.97 (s, CH_3), 4.15 (heptet, J = 6.2 Hz, $CH(CH_3)_2$), 4.29 (s, $CH_2C_6H_5$), 7.27 (s, $CH_2C_6H_5$). *Anal.* Calcd for $C_{11}H_{17}NOS$: C, 62.22; H, 8.55; N, 6.60; S, 15.10. Found: C, 62.43; H, 8.34; N, 6.38; S, 14.84.

Bis(*N*-benzyl-*N*-methylamine) Sulfide, 6c. Purified SCl_2 (7.7 g, 0.075 mol) was added dropwise to a cooled (−78°) stirred solution of benzylmethylamine (36 g, 0.3 mol) in petroleum ether (400 ml). After being allowed to react at −78° for 1 hr, the reaction mixture was allowed to warm to room temperature and filtered. The solvent was removed *in vacuo* and the crude product recrystallized from methanol: mp 37–38° (87% yield); nmr (toluene-d_8) δ 2.78 (s, CH_3), 2.58 (s, $CH_2C_6H_5$), 7.16 (s, $CH_2C_6H_5$). *Anal.* Calcd for $C_{16}H_{20}N_2S$: C, 70.55; H, 7.40; N, 10.28; S, 11.77. Found: C, 70.54; H. 7.35; N, 10.20; S, 11.81.

Bis(*N*-benzyl-*N*-methylamine) Trisulfide, 6d. A mixture of sulfur chlorides was obtained by treatment of sulfur monochloride with I_2 followed by distillation to obtain a fraction rich in S_3Cl_2. The mixture of sulfur chlorides (15 g, *ca.* 1 mol) was added dropwise to a cooled (0°) stirred solution of benzylmethylamine (48 g, 0.4 mol) in petroleum ether (500 ml). After reaction for 1 hr at 0°, the reaction mixture was filtered and the solvent removed *in vacuo*. The resulting mixture was chomatographed and the fraction corresponding to the trisulfide was recrystallized from hexane: mp 85–86° (35% yield); nmr (toluene-d_8) δ 2.54 (s, CH_3), 7.10 (s, C_6H_5). *Anal.* Calcd for $C_{16}H_{20}N_2S_3$: C, 57.11; H, 5.99; N, 8.32; S, 28.58. Found: C, 57.13; H, 6.09; N, 8.45; S, 28.73.

Registry No.—6a, 53370-27-7; **6b,** 53370-28-8; **6c,** 53370-29-9; **6d,** 53370-30-2; SCl_2, 10545-99-0; benzylmethylamine, 103-67-3; isopropyl alcohol, 67-63-0; chloroform-*d*, 865-49-6; toluene-d_8, 2037-26-5; tetramethylammonium chloride, 75-57-0; tetraethylammonium perchlorate, 2567-83-1.

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(2) Alfred P. Sloar Fellow.

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Vinylcyclopropanation of Olefins with Vinyldiazomethane

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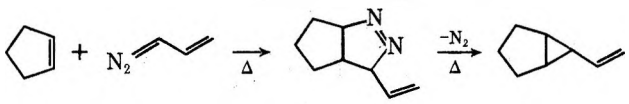
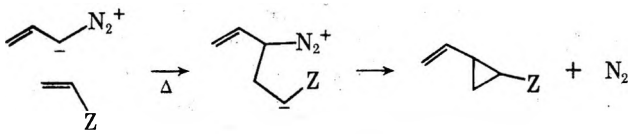
Received October 7, 1974

Vinylcyclopropanation of olefins by copper-catalyzed reaction with vinyldiazomethane is a short and convenient synthesis of vinylcyclopropanes. Though all copper salts examined cause decomposition of vinyldiazomethane with evolution of nitrogen, only a very few catalyze cyclopropanation. With *cis*- and *trans*-2-butenes, the catalyzed vinylcyclopropanation is stereospecific. Several pairs of isomeric vinylcyclopropanes were prepared and fully characterized. The more sterically congested endo isomer is favored in the reaction with cyclohexene in contrast with cyclopropanations with ethyl diazoacetate and trimethylsilyldiazomethane which both give almost exclusively the exo isomer. The more congested syn isomer is likewise preferentially formed in the reaction of vinyldiazomethane with vinylacetate.

We were confronted with the necessity of preparing a variety of vinylcyclopropanes in connection with another study. A very direct synthetic approach to these compounds is addition of vinylcarbene to the appropriate olefin. Diazo compounds are commonly used as precursors of carbenes and carbenoids.[1] Vinyldiazomethane reacts thermally with strained olefins,[2] or olefins with unsaturated electron-withdrawing substituents,[3] to give pyrazolines in moderate yields. The pyrazolines decompose with loss of



nitrogen to give vinylcyclopropanes in low yields. Direct production of vinylcyclopropanes in trace amounts without intervention of pyrazolines occurs in certain cases, namely unsymmetrical polarized olefins with unsaturated electronegative substituents. Vinylcarbene is not considered an intermediate in such reactions. Rather, a stepwise dipolar mechanism is postulated involving ionic addition to the olefin to give a zwitterionic intermediate which cyclizes by nucleophilic displacement of nitrogen.[3] In general, thermal



Z = CO_2CH_3, CN

reaction of vinyldiazomethane with olefins is not a preparatively useful synthesis of vinylcyclopropanes. Photolysis of diazo compounds generally induces loss of nitrogen and provides the corresponding carbenes.[1] However, vinyldiazomethane undergoes a photochemical cyclization to form pyrazolenine.[4] Copper salts are often used to catalyze cyclopropanation of olefins with diazo compounds.[1,5] Therefore we examined the copper-catalyzed reaction of vinyldiazomethane with olefins. We now report the successful application of this approach to the synthesis of a variety of vinylcyclopropanes.[6]

Results and Discussion

The efficacies of various catalysts were determined for the vinylcyclopropanation of cyclohexene with vinyldiazomethane under standard conditions (see Experimental Section). The results are summarized in Table I. The factors responsible for the observed differences in yield are not clear. All of the copper salts examined promoted the decomposition of vinyldiazomethane as evidenced by the evolution of nitrogen and disappearance of the red color of the diazo compound. Cupric trifluoromethanesulfonate and cupric hexafluoroacetylacetonate promote vinylcyclopropanation in the highest yield. Cupric trifluoroacetate also effectively catalyzes this reaction, although in lower yield. Other copper salts were ineffective even though they effectively catalyze cyclopropanations with other diazo compounds. Copper chloride is often used effectively for catalyzing the reaction of diazomethane with olefins.[7] Tri-*n*-butylphosphinecopper(I) iodide is an excellent catalyst for cyclopropanations with diazo esters.[8] The bis(di-*n*-butyl sulfide)copper(I) iodide complex catalyzes cyclopropanations with diazo ketones.[9]

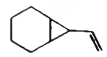
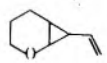
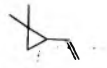
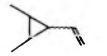
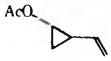
Table I
Yield of Vinylcyclopropanes in the Reaction of Vinyldiazomethane with Cyclohexene with Various Copper Salts as Catalyst

Catalyst	Yield, %
Cupric hexafluoroacetylacetonate	20
Cupric trifluoromethanesulfonate	40
Cupric trifluoroacetate	12
Tri-*n*-butylphosphinecopper(I) iodide	2
Bis(di-*n*-butyl sulfide)copper(I) iodide	2
Cuprous chloride	<2
Cupric carbonate	<1
Cupric sulfate (anhydrous)	<1

Optimum Catalyst to Diazo Ratio. The reaction between vinyldiazomethane and cyclohexene was conducted in the presence of varying amounts of cupric hexafluoroacetylacetonate (see Figure 1). The yield of vinylcyclopropane increases sharply as the relative amount of catalyst is increased until a ratio of about 20:1 of vinyldiazomethane to catalyst is reached. After leveling off, the yield decreases slightly as the relative amount of catalyst exceeds 10 mol %. Moreover, the use of larger amounts of catalyst is accompanied by the production of greater quantities of side products which are difficult to separate.

The observed deleterious effect of excessive quantities of catalyst is readily explained. Copper(II) salts are reduced by diazo compounds and yield copper(I) salts, which are the actual cyclopropanation catalysts.[5] Appreciably soluble copper(II) salts (copper hexafluoroacetylacetonate is appreciably soluble in olefin-containing solutions[10]) are reduced completely and an equivalent amount of diazo compound is destroyed. The observed decrease of yield at very low catalyst to diazo ratios may be due to destruction of the copper(I) catalyst by a similar though less rapid reduction by relatively large excesses of diazo compound. Also at lower catalyst to total vinyldiazomethane ratios, the concentration of diazo compound in the reaction mixture may

Table II
Preparative Scale Reaction of Vinyldiazomethane with Various Olefins

Olefin	Registry no.	Vinylcyclopropane	Registry no.	Yield, %	Catalyst
	110-83-8		53951-19-2	20	Cupric hexafluoroacetylacetonate
			53951-20-5	20	Cupric trifluoromethanesulfonate
	110-87-2		53951-21-6	24	Cupric trifluoroacetate
	1708-29-8		53951-22-7	13	Cupric hexafluoroacetylacetonate
	115-11-7		7736-30-3	20	Cupric hexafluoroacetylacetonate
				38	Cupric trifluoromethanesulfonate
	590-18-1		53951-23-8	22	Cupric trifluoromethanesulfonate
			54019-66-8	29	Cupric hexafluoroacetylacetonate
	624-64-6		54019-67-9	16	Cupric hexafluoroacetylacetonate
	108-05-4		53965-73-4	9	Cupric hexafluoroacetylacetonate
			53965-72-3		

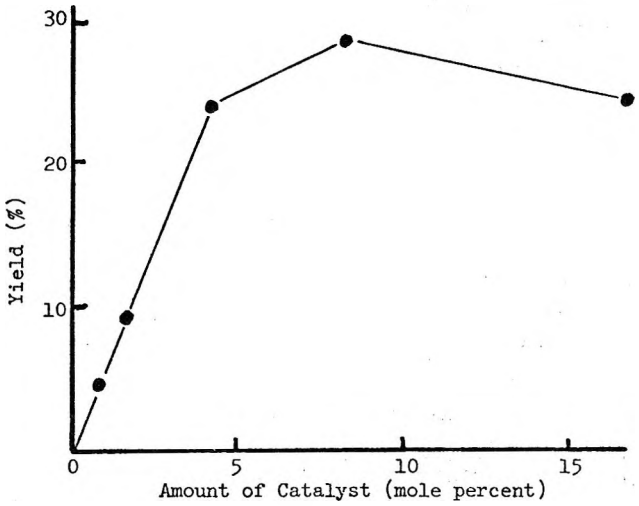
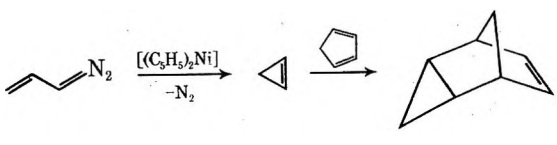


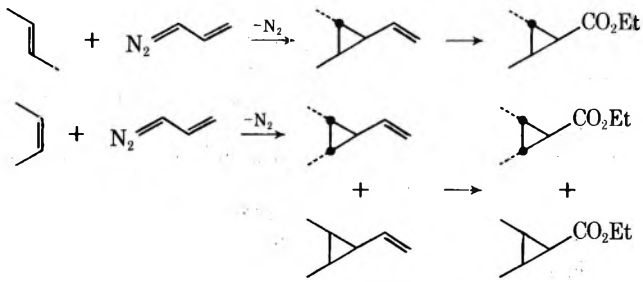
Figure 1. Vinylcyclopropane yield as a function of mole percent of catalyst in the reaction of cyclohexene with vinyldiazomethane.

build up owing to the low rate of catalytic reaction, and side reactions involving two molecules of diazo compound may become important.

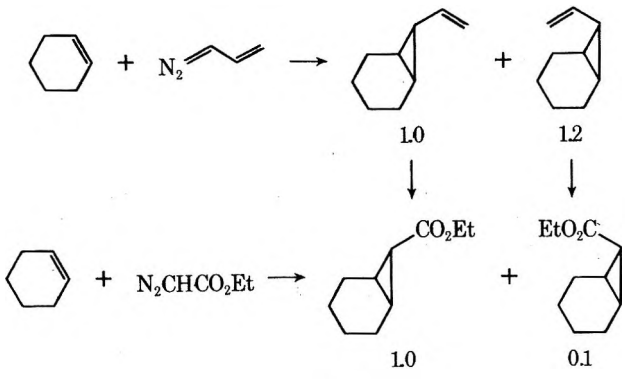
Preparative Vinylcyclopropanation. Many side reactions are expected to interfere with the vinylcyclopropanation of olefins with vinyldiazomethane. The products themselves are olefins and therefore are susceptible to undesirable further additions of carbenes. Vinyldiazomethane is unstable and rearranges to pyrazolenines (3*H*-pyrazoles).[4] However, we developed procedures which consistently gave solutions of vinyldiazomethane in pentane or cyclohexene in greater than 82% yield (see Experimental Section). The solutions decomposed slowly at 0°. After standing for 7 hr the yield decreased to 76% and after 48 hr it decreased to 63%. Finally, vinylcarbenes exhibit a general tendency to react intramolecularly to give cyclopropenes.[1] For example, vinyldiazomethane is converted to cyclopropene with loss of nitrogen under catalysis by nickelocene. In cyclopentadiene as solvent, *endo*-tricyclo[3.2.1.0^{2,4}]oct-6-ene is formed.[11] In spite of these many potential interfering side reactions, *isolated* yields of vinylcyclopropanes as high as 38% are obtained from copper salt catalyzed reaction of vinyldiazomethane with olefins. Thus, this synthetic approach may be the method of choice for the preparation of a variety of vinylcyclopropanes from readily available olefins, since it is very short and convenient, and the necessary reagents are readily available and inexpensive (see Table II).



Stereospecific Vinylcyclopropanation of 2-Butenes. Copper hexafluoroacetylacetonate catalyzes the reaction of vinyldiazomethane with *trans*-2-butene to give a single vinylcyclopropane product which exhibits two nonequivalent methyl doublets in its proton magnetic resonance spectrum. Similar reaction of *cis*-2-butene gives two isomeric vinylcyclopropyl products which each exhibit only one methyl doublet in their ^{1}H NMR spectra. The isomeric 1,2-dimethyl-3-vinylcyclopropanes were further identified as the expected products of stereospecific additions of vinylcarbene to the isomeric olefins by conversion to the respective ethyl 2,3-dimethylcyclopropanecarboxylates, which are identical with authentic samples.[5,12]

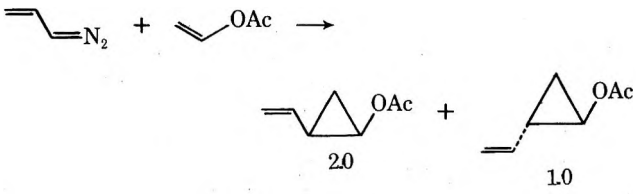


Stereochemical Course of Cyclohexene Vinylcyclopropanation. Both cupric hexafluoroacetylacetonate and trifluoromethanesulfonate catalyze the vinylcyclopropanation of cyclohexene with vinyldiazomethane to give two isomeric products in a ratio of 1.2:1.0. These isomers were characterized as *endo*- and *exo*-7-vinylbicyclo[4.1.0]heptane, respectively, by conversion to the known corresponding *endo*- and *exo*-7-carbomethoxybicyclo[4.1.0]heptanes.[13] This endo/exo ratio remains constant during the course of the addition of vinyldiazomethane to the reaction mixture. The ratio was found to be 1.22 ± 0.02 during addition of 10–100% of the total diazo compound. The observed preferential formation of an endo isomer is unusual. *Copper-catalyzed cyclopropanation of cyclohexene* with ethyl



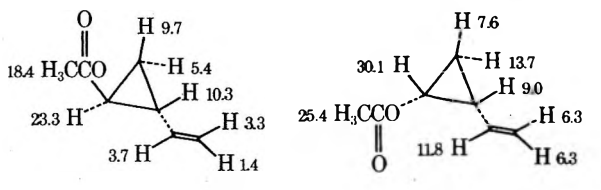
diazoacetate or with trimethylsilyldiazomethane favors production of the exo isomer by 0.10 and 0.11–1.00, respectively.[8a,14] Since the vinyl goup is less bulky than a carboethoxy or trimethylsilyl group, preferential formation of the more congested endo isomer of the vinyl derivative and the less congested exo isomer of the carboethoxy or trimethylsilyl may be simply the result of steric control.

Structural Characterization of Isomeric 1-Acetoxy-2-vinylcyclopropanes. The reaction of vinyldiazomethane with vinyl acetate is catalyzed by copper hexafluoroacetylacetonate. Two isomeric 1-acetoxy-2-vinylcyclopropanes are obtained in a ratio of 1.0:2.0 As in the case of the isomeric cyclohexene adducts discussed above, the major product is the more sterically congested syn isomer. This isomer, *cis*-1-acetoxy-2-vinylcyclopropane, was characterized by analysis of its ^1H NMR spectrum. Thus one proton on C-3 shows a coupling of 4.1 Hz with the proton α to the acetoxy group. This coupling constant is characteristic of

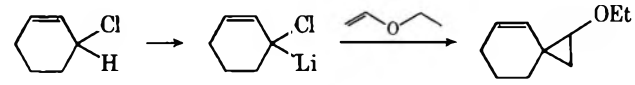


trans-vicinal protons.[15] The other proton on C-3 shows a coupling of 9.3 Hz with the allylic proton. This is characteristic of cis-vicinal protons.[15] Taken together, these facts imply a cis relationship between the vinyl and acetoxy groups. Confirmation of this assignment was obtained with the aid of a shift reagent.[16] Changes in proton chemical shifts were induced by europium(III) tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate. The extrapolated magnitudes of these shifts for a 1:1 mole ratio of acetoxyvinylcyclopropane to europium are indicated in Chart I. Thus, the shifts of the vinyl protons in the case of the cis isomer are two to four times greater than those in the trans isomer. All other comparisons, though less dramatic, unequivocally support the assigned structures.

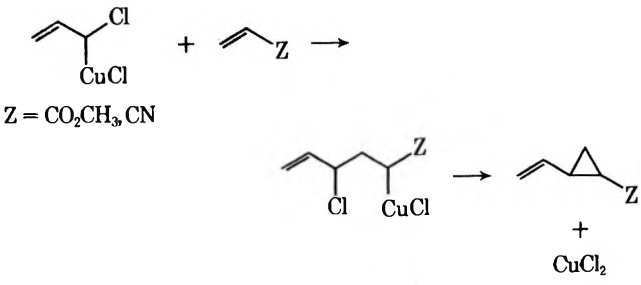
Chart I
Europium-Induced Molar Chemical Shift Changes for *cis*- and *trans*-1-Acetoxy-2-vinylcyclopropane



Comparison with Other Vinylcyclopropanation Reactions. Though allylic halides generally yield cyclopropenes upon α-lithiation, a single instance of the addition of a vinyl carbenoid to an olefin was observed recently. Thus α-lithiation of 3-chlorocyclohexene in the presence of ethyl vinyl ether produces a vinylcyclopropane.[17] It is not yet known whether this reaction proceeds with the stereospecificity characteristic of carbenoid additions as found in the copper-catalyzed reaction of vinyldiazomethane with unactivated olefins.



Recently vinylcyclopropanes were obtained by the reaction of 1,3-dichloropropene or allylidene chloride with copper(0) in the presence of α,β-unsaturated esters or nitriles.[18] It may be that these cyclopropanations involve Michael addition of copper(II) carbenoids followed by 1,3-elimination from the resulting β-chloroorganocopper(II) chloride intermediates. An activating group such as ester or nitrile appears necessary for these vinylcyclopropanations.



In contrast with copper-catalyzed vinylcyclopropanation of unactivated olefins with vinyl diazomethane, no examples of vinylcyclopropanation of unactivated olefins with the allylidene chloride–copper(0) reagent are known.

Experimental Section

General. Preparative gas–liquid phase chromatography was performed with a Varian Model 202B instrument. Proton magnetic resonance spectra were recorded with a Varian A-60A or HA-100 FT spectrometer with tetramethylsilane as an internal standard and CCl_4 as solvent. ^1H NMR spectral data are at 60 MHz unless otherwise indicated. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

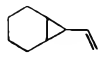
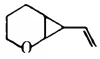
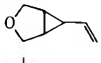
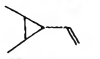
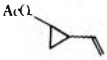
Materials. Olefinic reactants (gases) were Matheson reagent or Phillips pure reagent grade. Liquid olefinic reactants were reagent grade or purified by distillation prior to use. Pentane used as reaction solvent was purified by stirring over concentrated H_2SO_4 for a minimum of 24 hr, washed with saturated aqueous $NaHCO_3$ and then with water, dried ($MgSO_4$), and distilled. Ethyl allylnitrosocarbamate,[19] diazoethane,[20] cupric trifluoromethanesulfonate,[21] ethyl diazoacetate,[22] isomeric ethyl 2,3-dimethylcyclopropanecarboxylates,[12] and isomeric 7-carboethoxybicyclo[4.1.0]heptanes[13] were prepared by known procedures.

Vinyldiazomethane.[23] A methanolic solution of sodium methoxide (0.13 mol) was prepared under dry nitrogen by dissolving sodium metal in methanol (50 ml) in a 500-ml single neck round-bottom flask equipped with a West condenser. Pentane (200 ml) was added. The flask was shielded from light by wrapping with aluminum foil. The reaction mixture was cooled with an ice–water bath. A solution of ethyl allylnitrosocarbamate (7.9 g, 50 mmol) in pentane (100 ml) was added over 1 hr with a pressure-equalizing addition funnel which replaced the West condenser. The mixture was stirred for an additional 1.5 hr at 0° after completion of the addition. The resulting red solution was washed twice with cold aqueous 5% NaOH solution (100 ml). The dark red solution of vinyldiazomethane was dried over anhydrous KOH and stored at 0° shielded from light. *Caution!* Vinyldiazomethane is potentially explosive.

The yield of vinyldiazomethane (82–85%) was determined by measuring the volume of evolved nitrogen from reaction of an aliquot of diazo compound solution with an excess of *p*-nitrobenzoic acid in tetrahydrofuran.

General Vinylcyclopropanation Procedure. Preparative

Table III
Reaction Conditions for Preparative Scale (50 mmol) Vinylcyclopropanations and Conditions for Product Isolation and Isomer Separation

Vinylcyclopropane	(g) Catalyst[a]	Olefin, ml	Bp, °C (mm)	GLC column for isomer separation	Relative GLC retention times and assignment
	(0.7) $Cu(hfacac)_2$ (0.7) $Cu(OTf)_2$	300 300	60–68 (22)	SE-30[b] (125°)	1.00:1.21 exo endo
	(0.4) $Cu(OTFA)_2$	50	80–82 (15)	FFAP[c] (80°)	1.00:1.09
	(1.3) $Cu(hfacac)_2$	70	80–95 (70)	Not separated	
	(0.75) $Cu(hfacac)_2$ (0.75) $Cu(OTf)_2$	125 125	77–81	SE-30 (60°)	
	(0.75) $Cu(OTf)_2$ (1.0) $Cu(hfacac)_2$	75 100	88–95	SE-30 (47°)	1.00:1.44
	(1.0) $Cu(hfacac)_2$	100		SE-30 (50°)	
	(0.5) $Cu(hfacac)_2$	160	76–85 (50)	FFAP (115°)	1.00:1.15 trans cis

[a] $Cu(hfacac)_2$ = cupric hexafluoroacetylacetonate, $Cu(OTf)_2$ = cupric trifluoromethanesulfonate, $Cu(OTFA)_2$ = cupric trifluoroacetate. [b] Free fatty acid phase (Analabs) 20% on 60/80 Chromosorb P. [c] Silicone gum rubber–methyl (Analabs) 15% on 60/80 Chromosorb P.

scale reactions were conducted in a 500-ml round-bottom flask under a static atmosphere of nitrogen. The diazo compound solution (50 mmole) was added with a pressure-equalizing addition funnel. A bubbler filled with mineral oil was employed to detect the evolution of nitrogen during the reaction. In the case of gaseous olefins, a Dry Ice–acetone cold finger condenser was required. The reaction mixture was vigorously stirred magnetically while the solution of vinyldiazomethane was added dropwise over 1 hr to an excess of the olefin and sufficient catalyst to cause rapid disappearance of the red color of the vinyldiazomethane as it was added. Yields of vinylcyclopropanes are given in Table II. Reaction and isolation conditions are indicated in Table III. In the case of gaseous olefins, unreacted olefin was allowed to evaporate prior to work-up. The reaction mixture was washed with dilute aqueous ammonium hydroxide until the washes were colorless, then washed with water, and dried ($MgSO_4$). Solvents and excess olefin were removed by distillation and the products were isolated by distillation and preparative gas–liquid phase chromatography as indicated in Table III. Boiling ranges are uncorrected. In the case of vinylcyclopropanation of cyclohexene, the olefin was used in place of pentane as solvent for the vinyldiazomethane, and this solution was added dropwise to a suspension of catalyst in 5 ml of cyclohexene. *Caution!* Dihydropyran undergoes a violently exothermic polymerization in the presence of traces of cupric trifluoromethanesulfonate. This salt cannot be used for vinylcyclopropanation of highly nucleophilic vinyl ethers. The vinylcyclopropane products were characterized by their ^1H NMR spectra and by elemental analysis. Some products were further characterized by oxidative conversion to the corresponding carboethoxycyclopropanes, which were identified by ^1H NMR and GLC comparison with authentic samples. 1,1-Dimethyl-2-vinylcyclopropane was also prepared by another route starting from the corresponding carboethoxycyclopropane.

7-Vinylbicyclo[4.1.0]heptane. Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.57; H, 11.47.

Endo isomer had ^1H NMR δ 0.8–2.2 (11 H, ring protons), 4.5–5.3 (2 H, m, vinyl CH_2), 5.4–6.0 (1 H, m, vinyl CH).

Exo isomer had ^1H NMR δ 0.75–1.02 (2 H, cyclopropyl at C-1, C-6), 1.02–2.2 (9 H, ring protons), 4.5–5.0 (2 H, m, vinyl CH_2), 5.0–5.6 (1 H, m, vinyl CH).

These isomers were characterized as *endo*- and *exo*-7-vinylbicyclo[4.1.0]heptane, respectively, by ozonolysis–oxidation–ethylation and comparison of the product esters with authentic samples of *endo*- and *exo*-7-carboethoxybicyclo[4.1.0]heptane.[12] The olefin (40 mg) in glacial acetic acid (1 ml) and formic acid (0.5 ml) was stirred magnetically while an excess of ozone was bubbled through the reaction mixture. Then 30% hydrogen peroxide (1 ml) was added and the resulting mixture was boiled under reflux for 2 hr.[24] The product was extracted into ether (2 × 20 ml). The extract was washed with water and then extracted with saturated aqueous Na_2CO_3 solution. After acidification of the aqueous extract with HCl, the product was taken up into ether (20 ml). The ether solution was dried ($MgSO_4$) and then treated with an ether solution of diazoethane. Solvent was removed by rotary evaporation to yield crude ethyl ester.

1,1-Dimethyl-2-vinylcyclopropane. Anal. Calcd for C_7H_{12}: C, 87.42; H, 12.58. Found: C, 87.46; H, 12.50. This olefin was also prepared by an indirect route starting with ethyl 2,2-dimethylcyclopropanecarboxylate. Isobutylene (200 ml) was condensed into a 1-l. round-bottom flask equipped with a Dry Ice–acetone cooled cold finger condenser. The reaction mixture was stirred magnetically. Cupric trifluoromethanesulfonate (2 g) and ether (150 ml) were added. The addition of ether raised the boiling point of the mixture to 6°. Ethyl diazoacetate (10 g) was added slowly with a hypodermic syringe through a rubber serum cap. The resulting mixture was stirred for several hours as excess isobutylene was allowed to evaporate. The reaction mixture was then washed with dilute aqueous ammonium hydroxide until the washes were colorless, and then with water. After drying ($MgSO_4$), solvent was rotary evaporated and the residue distilled under reduced pressure to yield ethyl 2,2-dimethylcyclopropanecarboxylate (62%): bp 79–81° (40 mm); ^1H NMR δ 0.76 (1 H, dd, J = 4.0, 8.2 Hz, C-3), 1.03 (1 H, dd, J = 4.0, 5.0 Hz, C-3), 1.17 (3 H, s, methyl), 1.20 (3 H, s, methyl), 1.25 (3 H, t, J = 7 Hz, ester methyl), 1.42 (1 H, dd, J = 5.0, 8.2 Hz, C-1), 4.06 (2 H, q, J = 7 Hz, ethyl CH_2).

The ester (6 g) in ether (50 ml) was added to $LiAlH_4$ (3 g) in ether (150 ml) under dry nitrogen with mechanical stirring over 10 min. The resulting mixture was boiled under reflux for 1 hr. After cooling, water (3 ml) was cautiously added dropwise followed by aqueous 15% sodium hydroxide (3 ml) and then water (9 ml). The resulting white granular precipitate was removed by filtration and washed with ether. The filtrate and washings were concentrated by rotary evaporation and the residue was distilled under reduced pressure to give an alcohol, bp 50° (6 mm).

Chromium trioxide (60 g) was added over 5 min to a mechanically stirred solution of pyridine (49 ml) in dry methylene chloride (600 ml) in a 1-l. flask equipped with a pressure-equalizing addition funnel under an atmosphere of dry nitrogen. After stirring for an additional 15 min, the above alcohol in methylene chloride (50 ml) was added over 10 min. The resulting mixture was stirred for 15 min. The organic solution was decanted and the tarry residue was triturated thrice with 150-ml portions of ether. The combined organic solution was washed with 5% NaOH (3 × 150 ml), 5% HCl (150 ml), saturated aqueous $NaHCO_3$ (150 ml), saturated aqueous $CuSO_4$ (2 × 150 ml), and saturated aqueous NaCl (150 ml). After drying ($MgSO_4$), solvents were removed by fractional distillation and the residue distilled under reduced pressure to give 2,2-dimethylcyclopropanecarboxaldehyde (76% from the ester): bp 51–61° (45 mm); ^1H NMR δ 0.40–0.59 (2 H, m, C-3), 0.76 (3 H, s, CH_3), 0.82 (3 H, s, CH_3), 0.94–1.46 (1 H, m, C-1), 9.36 (1 H, d, –CHO).

n-Butyllithium in hexane (23.0 ml of 1.65 *N*) was added to a magnetically stirred suspension of methyltriphenylphosphonium bromide (14.4 g) in dry tetrahydrofuran (60 ml) under an atmosphere of dry nitrogen at 0°. After stirring for 30 min, the above aldehyde in tetrahydrofuran (10 ml) was added dropwise over 2 min. The resulting mixture was stirred at room temperature for 20 min. Pentane (100 ml) was added and the mixture was washed with water (4 × 100 ml), dried ($MgSO_4$), and concentrated by distillation through a 20-cm Vigreux column. The residue was distilled to give 1,1-dimethyl-2-vinylcyclopropane (24% overall from ethyl diazoacetate) which was identical (^1H NMR) with a sample prepared by direct vinylcyclopropanation of isobutylene: ^1H NMR δ 0.25–0.75 (2 H, m, C-3), 1.03 (3 H, s, methyl), 1.08 (3 H, s, methyl), 1.29 (1 H, dd, J = 5.5, 8.0 Hz, C-2), 4.75–5.15 (2 H, m, vinyl), 5.15–6.0 (1 H, m, vinyl).

7-Vinyl-2-oxabicyclo[4.1.0]heptane. Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.41; H, 9.72. The product probably is a mixture of isomers, but these were not separated: ^1H NMR δ 0.75–2.2 (6 H, C-4, C-5, C-6, C-7), 2.9–3.8 (3 H, C-1, C-3), 4.6–5.4 (2 H, m, vinyl CH_2), 5.4–6.4 (1 H, m, vinyl CH).

6-Vinyl-3-oxabicyclo[3.1.0]hexane. Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.19; H, 9.20. The product probably is a mixture of isomers, but these were not separated: ^1H NMR δ 1.2–1.9 (3 H, cyclopropyl), 3.83 (4 H, s, C-2, C-4), 4.9–5.3 (2 H, m, vinyl CH_2), 5.4–6.0 (1 H, m, vinyl CH).

1-Acetoxy-2-vinylcyclopropane. Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.44; H, 7.87.

Cis isomer had ^1H NMR (100 MHz) δ 0.64–0.88 (1 H, dt, J = 6.6, 6.6, 4.1 Hz, C-3 trans to C-1 proton), 0.97–1.22 (1 H, dt, J = 9.3, 6.5, 6.5 Hz, C-3 cis to C-2 proton), 1.48–1.84 (1 H, m, C-2), 1.99 (3 H, s, acetate CH_3), 4.06–4.29 (1 H, dt, J = 4.1, 6.5, 6.5 Hz, C-1), 4.88–5.25 (2 H, m, vinyl CH_2), 5.30–5.68 (1 H, m, vinyl CH).

Trans isomer had ^1H NMR (100 MHz) δ0.71–1.10 (2 H, m, C-3), 1.40–1.76 (1 H, m, C-2), 1.95 (3 H, s, acetate CH_3), 3.83–4.02 (1 H, m, C-1), 4.84–5.14 (2 H, m, vinyl CH_2), 5.30–5.78 (1 H, m, vinyl CH).

Various quantities of europium(III) tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate (0–0.2 equiv) were added to the above solutions. The induced chemical shift changes extrapolated to a 1:1 mole ratio are indicated in Chart I.

***cis*- and *trans*-3-Vinyl-*cis*-1,2-dimethylcyclopropane.** Anal. Calcd for C_7H_{12}: C, 87.42; H, 12.58. Found: C, 87.13; H, 12.42. Two isomers were obtained in a ratio of 0.27:1.00, respectively, for the products of relative GLC retention times of 1.00 and 1.44 on an SE-30 column.

Minor isomer had ^1H NMR δ 0.5–1.1 (3 H, cyclopropyl), 1.06 (6 H, d, J = 3.8 Hz, C-1, C-2), 4.5–5.1 (2 H, m, vinyl CH_2), 5.1–5.7 (1, H, m, vinyl CH).

Major isomer had ^1H NMR δ 0.9–1.7 (3 H, cyclopropyl), 1.01 (6 H, d, J = 1.4 Hz, CH_3 at C-1, C-2), 4.8–5.8 (3 H, m, vinyl).

3-Vinyl-*trans*-1,2-dimethylcyclopropane. Anal. Calcd for C_7H_{12}: C, 87.42; H 12.58. Found: C, 87.40; H, 12.55. ^1H NMR δ 0.2–0.7 (3 H, m, cyclopropyl) 0.97–1.12 (6 H, two doublets, J = 5.4 Hz, CH_3 at C-1, C-2), 4.71–5.15 (2 H, m, vinyl CH_2), 5.18–5.81 (1 H, m, vinyl CH).

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—Vinyldiazomethane, 2032-04-4; cupric hexafluoroacetylacetonate, 14781-45-4; cupric trifluoromethanesulfonate, 34946-82-2; cupric trifluoroacetate, 16712-25-7; ethyl diazoacetate, 623-73-4; ethyl 2,2-dimethylcyclopropanecarboxylate, 16783-11-2; 2,2-dimethylcyclopropanecarboxaldehyde, 26119-44-8; europium(III) tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate, 17631-68-4.

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Deoxygenation of Aryl Nitro Compounds with Disilanes

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Received September 19, 1974

Disilanes have been found to represent a new class of deoxygenating agents for aryl nitro compounds. Semiquantitative investigation of the effect of disilane structure on the deoxygenation of 2-nitrobiphenyl (1) at 240°, which yielded 2-aminobiphenyl (3) and carbazole (4), indicated only moderate reduction rate differences among those disilanes studied, with hexachlorodisilane (Si_2Cl_6) and hexaphenyldisilane (Si_2Ph_6) being the most and least reactive, respectively. In contrast, the relative ratio of 4:3 was markedly dependent on disilane structure and varied between limits of ~70:1 and 1:35 for reduction with, respectively, cyclic 1,2-disilacyclopentene derivative 6 and Si_2Cl_6. Deoxygenation of nitrobenzene (7a), o-nitrotoluene (7b), and *p*-nitrotoluene (7c) with hexamethyldisilane (Si_2Me_6) gave their corresponding amines and azo coupling products, with $\Delta G^{\ddagger}_{220°} = 41$ kcal/mol for the pseudo-first-order reduction of 7a in excess Si_2Me_6. Qualitative comparison of Si_2Me_6 deoxygenation rates for 1 and 7a–c at 240° revealed that relative substrate reactivities were not in accord with expectations based on simple steric considerations. Failure of 2-nitrosobiphenyl to undergo deoxygenation by Si_2Me_6 has led to the suggestion that disilane reduction of 1 and, by extension, other nitro aromatics does not proceed in a stepwise fashion *via* nitroso intermediates. Mechanisms which accommodate this restriction and account for the observed stoichiometry and products are discussed in terms of possible transient nitrene species. Attempts to carry out low-temperature photochemical deoxygenation of 1 with Si_2Me_6 proved unsuccessful.

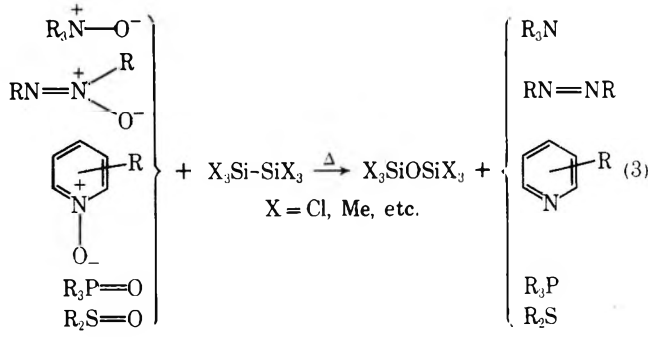
Deoxygenation of nitro compounds (RNO_2) with appropriate reducing agents can, in principle, lead to generation of nitrenes (R$\ddot{N}$:) as transitory reaction intermediates (eq 1). Early attempts to utilize metallic salts[2] for this reduc-

$$RNO_2 \longrightarrow R\ddot{N}: \longrightarrow \text{products} \qquad (1)$$

tion process have been followed by more recent work with metal carbonyls;[3] however, the majority of synthetic[4] and mechanistic[5] investigations related to eq 1 have employed Cadogan's[4a] phosphine method (eq 2) to effect nitro group

$$RNO_2 + 2R_3'P \longrightarrow R\ddot{N}: + 2R_3'PO \qquad (2)$$

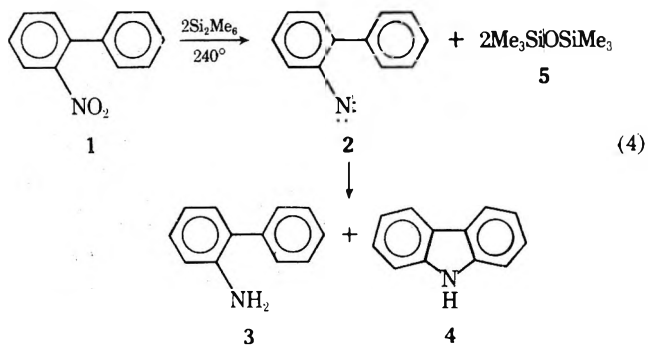
deoxygenation. The proven ability of disilanes ($X_3Si–SiX_3$) to function as efficient reducing agents for various organic[6a,c,7] (and inorganic[8]) nitrogen oxides, as well as phosphine oxides[6a,6b] and sulfoxides[6a] (eq 3), suggested to us



that disilanes might also serve as useful deoxygenating agents for nitro compounds.[9] In addition to the possibility that such a process might hopefully proceed at temperatures lower than those necessary with known nitro group reducing reagents, other advantages were envisaged. Thus, use of disilanes would preclude complications due to extensive formation of unwanted phosphorimidate ($RN=PR_3'$) side products,[4b,10] which oftentimes accompany reduction with phosphorus reagents, and limitations placed on deoxygenation of multifunctional nitro compounds due to the well-known[11] reactivity of phosphines toward halide, epoxide, and keto groups might also be removed by use of nonnucleophilic disilane reagents. With these potential benefits in mind, we undertook the exploratory investigation of nitro group reduction by disilanes that is presented in the following sections.[12]

Results and Discussion

Deoxygenation of 2-Nitrobiphenyl with Hexamethyldisilane. Commercially available hexachlorodisilane (Si_2Cl_6) has been generally used in disilane deoxygenation studies;[6] however, the somewhat detrimental characteristics (H_2O and O_2 sensitivity) of this reagent relative to hexamethyldisilane (Si_2Me_6), which is readily prepared[13] and convenient to handle, led to selection of Si_2Me_6 for initial evaluation. Our choice, like others,[3a,4a,14] of 2-nitrobiphenyl (1) as a prototypal substrate for deoxygenation was prompted by the expectation that the nitrene (or nitrenoid) intermediate derived therefrom, *viz.* 2-biphenylylnitrene (2), would produce thermally stable products from relatively well-defined reaction modes: 2-aminobiphenyl (3) from H abstraction and carbazole (4) *via* formal intramolecular C–H bond insertion (*cf.* eq 4). Nitroalkanes were



not considered in the present study since similar reaction modes with alkylnitrenes possessing α-hydrogens are generally low-yield events, due to efficient competition by intramolecular α-hydrogen abstraction[15] yielding imines which subsequently undergo rapid polymerization.

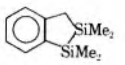
As indicated by eq 4, deoxygenation is simply achieved by heating an *o*-dichlorobenzene (ODCB) solution of 1 (0.7 *M*) containing 2 molar equiv of Si_2Me_6 (1.4 *M*) at 240° for *ca.* 2 hr, using a sealed (*in vacuo*) glass ampoule. Analysis (vpc) of the darkened reaction mixture revealed that only a small percentage (~10%) of unchanged starting material remains under these conditions and that near-quantitative production of hexamethyldisiloxane (5) occurred. Work-up led to isolation of 4 (42%) as the major product and a small amount of 3 (4%). Only a trace amount (<1%) of an addi-

Table I
Deoxygenation of 2-Nitrobiphenyl (1) with Various Reagents

Reagent	Reagent:1, molar ratio	Conditions	Product, %[a] 4	3
Si_2Me_6[b]	2	240°, 2.5 hr	42	4
$(EtO)_2PMe$[c]	4	100°, 2 hr	85	Not reported.
FeC_2O_4[d]	13	210°, 0.5 hr	63	Not reported
$Fe(CO)_5$[e]	1.4	142°, 24 hr	15	58

[a] Isolated yield. [b] This work. [c] Reference 5c. [d] Ferrous oxalate, ref 14. [e] Reference 3a.

Table II
Deoxygenation of 2-Nitrobiphenyl (1) with Disilanes[a]

Disilane	Registry no.	Unreacted 1, %[b]	Product, %[b] 4	3
Si_2Ph_6	1450-23-3	100[c]		
Si_2Me_6	1450-14-2	90	4	1
$Si_2Me_5(OPh)$	32286-27-4	85	6	1
$Si_2Me_5(Ph)$	1130-17-2	27	37	7
	40662-22-4	22	71	1
Si_2Cl_6[d]	13465-77-5	13	10	47

[a] Sealed ampoule with *o*-dichlorobenzene (ODCB) solvent; [1] = 0.7 *M*; [disilane] = 1.4 *M*; 240°, 1.5 hr. [b] Determined by quantitative vpc after addition of triphenylmethane internal standard and corrected for thermal conductivity differences. [c] 95% after 15 hr, with 5% 4 and no detectable (<1%) 3. [d] Vpc analysis preceded by alkaline work-up of reaction mixture.

tional and as yet unknown compound was detectable by vpc.

More accurate appraisal of the true product distribution by vpc techniques gave 86% conversion of 1 into 68% 4 and 8% 3, with ~20% material loss attributable to intractable "tars," which were evident by tlc and are commonly encountered[4] in nitrene chemistry. Appropriate control experiments confirmed that neither starting material 1 nor a 1:1:2 mixture of 3:4:Si_2Me_6 (or 3:4:5) react significantly under the reduction conditions employed. These facts suggest that the deoxygenation stoichiometry is as shown in eq 4, which is a conclusion consistent with earlier studies[6a,7] indicating that each Si–Si linkage in a polysilane is capable of extruding one oxygen atom from the oxidant.

Comparison of the above data with typical results reported for other deoxygenating agents (Table I) indicated that Si_2Me_6 competes reasonably well with ferrous oxalate and is superior to $Fe(CO)_5$ for production of the synthetically more significant ring closure product 4, but is not as efficient as the phosphonite reagent.

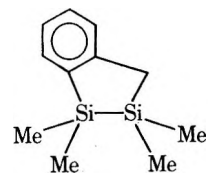
Attempts to investigate possible acceleration of the disilane deoxygenation rate of 1 by solvent variation were restricted by the unavailability of media which are considered to be strongly solvating but yet inert toward Si_2Me_6 at elevated temperatures. This dual criterion excludes solvents such as hexamethylphosphoramide (HMPA) and dimethyl sulfoxide (DMSO), as well as various alcohols. Consequently, it was not surprising that substitution of ODCB with either *n*-nonane, *p*-xylene, chlorobenzene, or bromobenzene, which are all relatively nonpolar substances, resulted in little or no improvement on reduction velocity.[16]

Modification of Disilane Structure. Variously substituted acyclic disilanes (Table II) and the novel 1,2-disilacyclopentene derivative 6[17] were next explored in order to (a) assess those structural features which might afford increased deoxygenating capacity toward 1 and (b) possibly elucidate mechanistic aspects of the reduction under consideration. Moreover, there has been only one systematic investigation[7] of disilane structure with regard to deoxygenation potency, and this was primarily restricted to remote electronic effects of ring substituents in phenoxypentamethyldisilane [$Si_2Me_5(OPh)$] derivatives.

Table III
Deoxygenation of Aryl Nitro Compounds with Si_2Me_6[a]

Compd	Rxn time, hr	Unreacted compd, %[b]	Products: Amine (%)	Azo (%)
1	13	0	4 (67[c])	Not determined
7a	43	16[c]	8a (22[c])	9a (11[c])
7b	42	22	8b (14)	Not determined
7c	45	50	8c (30)	9c (10)

[a] Sealed ampoule; molar ratio compound:Si_2Me_6 = 1:3, no solvent; 240°. [b] Determined by quantitative vpc with addition of authentic material, unless specified otherwise. [c] Isolated yield.



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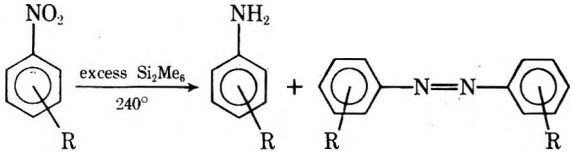
The relative amounts of unreacted 1 listed in Table II indicate that only moderate deoxygenation rate differences obtain for the disilanes studied, with the exception of hexaphenyldisilane (Si_2Ph_6), which was effectively inert under the specified standard reaction conditions.[18] These *roughly* comparable deoxygenation rates for 1 stand in contrast to dramatic disilane reduction rate inequities which may be extracted from available literature data. Thus, we estimate that $Si_2Me_5(OPh)$ is on the order of 1000 times more reactive than Si_2Me_6 toward conversion of trimethylamine oxide to trimethylamine[7] and that Si_2Cl_6 is capable of reducing phosphine oxides ~500 times faster than Si_2Me_6.[6a] It may therefore be concluded that those factors which render $Si_2Me_5(OPh)$ and Si_2Cl_6 considerably more reactive than Si_2Me_6 in amine and phosphine oxide deoxygenations, respectively, are unimportant in the present context. In similar fashion, the enhanced reactivity (>95-fold) of "strained"[17,19] disilane 6 over acyclic model compound $Si_2Me_5(Ph)$ toward Si–Si bond oxidation by *m*-chloroperbenzoic acid is not translated into a comparable deoxygenation rate difference toward 1 (*cf.* Table II).

Deoxygenation of Other Nitro Compounds with Hexamethyldisilane. Reactions at the ortho position in biphenyl systems may, on account of steric effects, be subject to pronounced rate retardation. It was of interest, therefore, to determine whether sterically less encumbered nitro groups, relative to that in 1, undergo disilane deoxygenation under more mild reaction conditions.

Reduction of 7a–c with Si_2Me_6 (eq 5) gave the expected



7 8 9

+ Si_2OMe_6 (5)

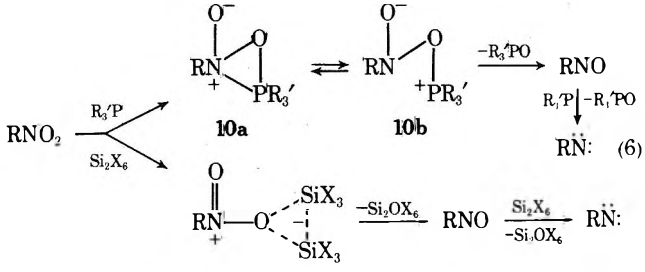
a, R = H; b, R = *o*-Me; c, R = *p*-Me

amines as major products in addition to somewhat lower yields of azo coupling products (**9**) (Table III). However, in contrast to expectations based on simple steric arguments, comparison of reaction times and amounts of unreacted starting material listed in Table III for **1** *vs.* **7a** and **7c** reveals that deoxygenation of the more accessible nitro groups offered by **7a** and **7c** is actually slower than that for **1**. Unimportance of steric effects is similarly indicated by comparison of the data tabulated for **7b** and **7c**, since the crowded *o*-NO_2 group in the former system undergoes more extensive reduction than its para-positioned counterpart in **7c**. At this point, we can only speculate that "electronic factors" may play a dominant role in governing relative disilane deoxygenation rates.

Causative factors underlying the production of **9** are discussed in a following section dealing with mechanism.

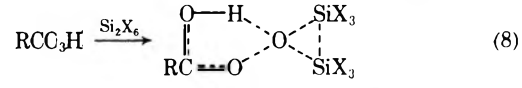
Kinetic and Mechanistic Considerations. The kinetics for deoxygenation of aryl nitro compounds with disilanes were briefly studied using **7a** and Si_2Me_6 (20-fold molar excess) as model reactants. The pseudo-first-order rate constant (k') calculated for disappearance of **7a** from duplicate runs is $k'_{220°} = 5.6 \pm 0.1 \times 10^{-6}$ sec^{-1} ($\tau_{1/2} \simeq 34$ hr), which corresponds to $\Delta G^{\ddagger}_{220°} = 41$ kcal/mol. This value for $\Delta G^{\ddagger}$ is significantly lower than the ~51 kcal/mol energy of activation reported for thermal decomposition of **7a**[20] and other[21] aromatic nitro compounds into aryl and NO_2 radicals *via* initial C–N bond homolysis.[21,22] These facts, in conjunction with the demonstrable thermal stability of Si_2Me_6 under the present reaction conditions, lead us to conclude that free-radical disilane deoxygenation paths initiated by C–N and/or Si–Si bond fission are not likely.

Mechanistic studies of nitro group deoxygenation with phosphorus reagents have prompted the suggestion[5a-c] of a stepwise process (eq 6) involving monodeoxygenation of RNO_2 *via* **10** to produce nitroso intermediates (RNO), which then undergo relatively rapid deoxygenation to generate nitrenes (or nitrenoids). An analogous series of transformations (eq 7) is reasonable for disilanes, wherein **11** is similar to the intermediate (**12**) postulated[23] for disilane oxidation by peracids (eq 8).



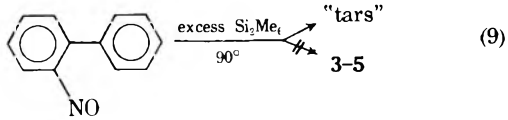
(6)

(7)



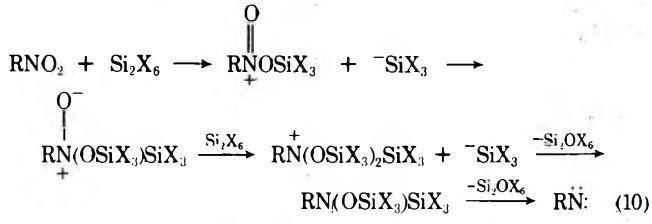
(8)

We have investigated the above possibility and have found that 2-nitrosobiphenyl (**13**) suffers essentially complete decomposition to mainly "tars," *without* forming detectable amounts of **3** or **4**, when heated at only 90° (19 hr) in ODCB containing a 20-fold molar excess of Si_2Me_6 (eq 9). These observations, coupled with high (80–90%) material balances obtained for Si_2Me_6 deoxygenation of **1**, militate against the intermediacy of **13** during reduction of **1** with disilanes and, hence, eq 7 or any other monodeoxygenation variant thereof.[24]

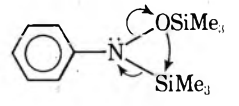


(9)

An alternative deoxygenation scheme, which bypasses nitroso compound intermediacy and is a simple extension of the disilane reduction mechanisms previously considered[6a,7] for amine oxides, is shown in eq 10. In this scheme

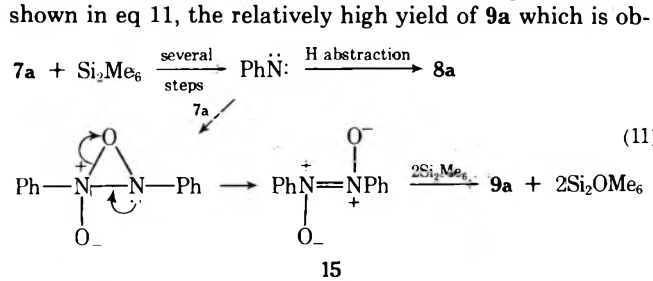


(10)



initial nucleophilic attack[7] of RNO_2 at silicon and concomitant Si–Si bond heterolysis is pictured as being followed by a sequence of steps which features ultimate nitrene generation *via* α-elimination of disiloxane (Si_2OX_6) from bis(silyl)hydroxylamine intermediate **14**. We have recently obtained evidence that supports the feasibility of this novel "α-deoxysilylation" proess[25,26] (**14** → RN̈: + Si_2OX_6) and demonstrates, *inter alia*, that expulsion of Si_2OMe_6 from **14a** takes place rapidly ($\tau_{1/2} \simeq 4$ hr) at only ~100°, which is far below those temperatures needed for nitro group reduction by disilanes. Thus, to the extent that eq 10 actually reflects the mechanism for RNO_2 deoxygenation by disilanes, we conclude that the rate-limiting step occurs prior to fragmentation of **14**.

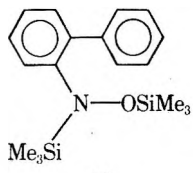
In an attempt to obtain more direct evidence for the involvement of **14** in the present reduction studies, **14a** was pyrolyzed in a threefold molar excess of Si_2Me_6 at 240°, which are the same conditions listed in Table III for Si_2Me_6 deoxygenation of **7a**. As expected on the basis of eq 5 and 10, **14a** yielded **8a** and **9a**; however, in contrast to the *ca.* 2:1 ratio of **8a**:**9a** obtained from **7a**, compound **14a** produced a *ca.* 4:1 mixture of these common products. As shown in eq 11, the relatively high yield of **9a** which is observed with **7a** may be rationalized by assuming that formation of **9a** involves addition of phenylnitrene to unreacted **7a**[29] followed by deoxygenation of **15**;[30] a similar path in the aforementioned study with **14a** is not operative. Consistent with this mechanistic rationalization, it was found that heating an equimolar mixture of **14a** and **7a** with Si_2Me_6 results in a substantial increase in the relative amount of **9a**, *viz.* **8a**:**9a** ≃ 1:1.



(11)

Comparative studies of **1** and Si_2Me_6 *vs.* **16**, which were considered as an additional probe for the validity of eq 10, have been foiled by our inability to prepare **16** *via* bis-trimethylsilylation of its unusually unstable[31] precursor, 2-biphenylylhydroxylamine.[32]

We note that while the thermal instability of **14a** under reaction conditions needed for Si_2Me_6 deoxygenation of **7a**



16

precludes a search for residual **14a** expected from **7a** and Si_2Me_6 on the basis of eq 10, derivatives of **14** where R = alkyl and X = Me have been shown[25] to require fragmentation temperatures (~200°) which approach those presently reported (220–240°) for deoxygenation. Consequently, disilane deoxygenation studies with nitroalkanes, which we are pursuing, may lead to isolation of derivative compounds with structure **14** and thereby provide partial support for the heuristic mechanism represented by eq 10.

Unequivocal mechanistic conclusions, especially with regard to the question of nitrene intermediacy, are beyond the scope of the present exploratory study and a detailed interpretation of the variable product ratios listed in Table II would be premature. By way of a starting point and for the sake of simplicity we have assumed, nevertheless, that a nitrene intermediate is produced by disilane deoxygenation of **1** and that the relative proportion of **4** and **3** is qualitatively indicative of singlet and triplet participation, respectively, in the reaction manifold. The uniquely high percentage of triplet product **3** produced by Si_2Cl_6 (despite the absence of abstractable H atoms), relative to the organodisilanes, can be accounted for on the basis of a "heavy atom effect" associated with the chlorine nuclei in Si_2Cl_6. Such an effect could accelerate crossing of initially produced singlet **2** to triplet **2** by efficient intermolecular interactions immediately following nitrene generation (eq 10).[33]

To test the preceding hypothesis, deoxygenation of **1** with 2 molar equiv of **6**, which had produced the highest **4**:**3** ratio (71:1), was carried out (240°, 1.5 hr) in the presence of 4 molar equiv of CCl_4 as a potential heavy atom donor. Expectations for a CCl_4-induced increase in the relative proportion of **3** over **4** were confirmed by our finding that **4**:**3** = 1:35. Control reactions (see Experimental Section) demonstrated that this product ratio change was not due to selective decomposition of **4** by CCl_4.

If heavy atom effects associated with Si_2Cl_6 and CCl_4 do play a role in the deoxygenation of **1**, the inefficiency of ODCB and other aryl halides that we have used as solvents toward inducing similar effects is not understood.[33]

Attempted Photochemical Deoxygenations with Hexamethyldisilane. Ultraviolet absorption by nitroaromatics in the region of ~300 mμ is generally ascribed to an $n \rightarrow \pi^*$ transition which produces a short-lived photoexcited state.[36] The diradical character and increased reactivity expected for this excited state species is further believed to manifest itself in bimolecular photochemical transformations with a vaiety of reaction partners that are not observed under thermal conditions.[36] We have therefore explored the possibility of photoinduced NO_2 group reduction[37] with disilanes; however, results obtained with **1** and Si_2Me_6 as a model system were discouraging (see Experimental Section).

Conclusions

Aside from fundamental mechanistic questions which remain unanswered, the present results clearly demonstrate that deoxygenation of nitro compounds can be accomplished with disilane reagents. Our results also suggest that reaction temperatures necessary for these deoxygenations may severely limit practical applications earlier envisaged for this new method in organic synthesis. Development of more reactive disilanes to overcome this current restriction is in progress.

Experimental Section[38]

Preparation of Disilanes. Hexachlorodisilane was purchased from Alfa-Ventron and was used under anhydrous and oxygen-free conditions without further purification. The procedure of Wilson and Smith[13] afforded Si_2Me_6 containing ≤~5% contamination by Si_2OMe_6 and "xylenes" (vpc, column A, 60°, 60 ml/min). Purified Si_2Ph_6 was obtained (50%) by slow recrystallization (hot benzene) of crude material that was prepared (85%) according to literature directions.[39] Phenoxypentamethyldisilane[7] (bp ~60°, 1 mm) was synthesized from chloropentamethyldisilane[40] by analogy to standard procedures[41] and was purified by preparative vpc with column A (150°, 60 ml/min). Standard reaction of phenylmagnesium bromide with an equimolar amount of chloropentamethyldisilane gave crude $Si_2Me_5(Ph)$,[42] which was purified in the same manner as $Si_2Me_5(OPh)$. Compound **6** was synthesized according to procedures described elsewhere[17] and was purified[17] prior to use.

Nitro Compound Deoxygenation with Disilanes. General Procedures. Vpc scale reaction mixtures (~0.2–0.3 ml total volume) were sealed (*in vacuo*) in thick-walled Pyrex tubes before heating in a calibrated, preequilibrated, Büchi ("Kugelrohr") hot air bath furnace. Reaction mixtures which were heterogeneous at room temperature were found to be homogenous at temperatures (200–240°) required for reduction. Preparative scale reactions were run in the same manner as vpc scale studies using an appropriate number of glass tubes. *Caution:* in all cases a ratio of tube volume to liquid volume (at room temperature) of *ca.* 4–5 was used without incident, except for one spurious tube explosion with **1** and Si_2Me_6 in *o*-dichlorobenzene (ODCB). Additional details are reported in Tables I–III and under specific headings which follow.

Deoxygenation of 2-Nitrobiphenyl (1) with Si_2Me_6. Vacuum (0.3 mm) short-path distillation of a reaction mixture, which was obtained by heating **1** (50 mg, 0.25 mmol) and Si_2Me_6 (0.1 ml, 0.5 mmol) in ODCB at 240° for *ca.* 2 hr, led to isolation of an oil (fraction A, bp 50–100°) and a less volatile solid (fraction B, bp 100–140°). Tlc [silica gel PF-254, petroleum ether (bp 30–60°)–ether (90:10)] comparison with authentic materials indicated that fractions A and B were **3** and **4**, respectively. Thick-layer chromatography of fraction A, followed by recrystallization from ethanol, gave pure **3** (4 mg, 4%), mp 46°, which was positively identified by ir and vpc comparisons with genuine **3** (mp 47–48°) prepared from zinc reduction of **1** according to the method of Kuhn.[43] Recrystallization of fraction B from CH_2Cl_2–petroleum ether (bp 30–60°) yielded pure **4** (35 mg, 42%) with melting point, ir, and vpc characteristics identical with those of purified commercial material (mp 243°).

Quantitative vpc analysis (column A, 60°, 60 ml/min) of a duplicate reaction mixture indicated a *ca.* 90% yield of Si_2OMe_6, based on the amount of reacted **1** (86%). The latter quantity and corrected yields for **3** (8%) and **4** (68%) were determined by vpc (column D, 170°, 60 ml/min) after addition of triphenylmethane internal standard. Material balances in this and subsequent runs were between 80 and 90%; slow-eluting dark-colored "tars" were evident by tlc, and a minor (~1%) unidentified component eluted (vpc) between **1** and triphenylmethane.

Relative Disilane Deoxygenation Rates for 1. Solutions of **1** (0.7 *M*) with the various disilanes (1.4 *M*) listed in Table II were heated at 240 ± 5° for 1.5 hr according to the above general procedures. Quantitative vpc analyses (column D, 170°, 60 ml/min) for all of the organodisilanes were carried out after dissolution of solids in CH_2Cl_2 and addition of triphenylmethane internal standard; the presence of unreacted disilane was confirmed by vpc. In the case of Si_2Cl_6, vpc analysis of the reaction mixture was preceded by dilution with CH_2Cl_2 and then vigorous stirring with 20% aqueous potassium hydroxide solution. Control reactions demonstrated that **1**, **3**, and **4** are not effected by this hydrolysis procedure,[6a] which removed corrosive and highly reactive silicon-based compounds. Results are summarized in Table II. Vpc precision was judged to be *ca.* ±5% and duplicate runs with **1** and Si_2Me_6 gave *ca.* ±5% relative precision error for the yields of **3**, **4**, and unreacted **1**. Control studies with **1** and Si_2Me_6 demonstrated that doubling the usual tube volume:liquid volume ratio (*vide supra*) did not significantly effect the extent of reaction or the ratio of **3**:**4**.

Deoxygenation of Other Nitroaromatics with Si_2Me_6. Vpc analysis (column B, 100°, 60 ml/min) of a solution of nitrobenzene (**7a**) (0.2 ml, 2 mmol) in Si_2Me_6 (1.2 ml, 6 mmol) that was heated at 240° for 43 hr indicated a 1:1 ratio of **8a** and unreacted **7a**.

These vpc component identifications were confirmed by Kugelrohr distillation of the reaction mixture to give an oil (bp 30–150°, 160 mm) from which **8a** (22%) and **7a** (16%) were collected by preparative vpc (column C, 135°, 60 ml/min) for ir comparisons with genuine samples. Column chromatography [silica gel, petroleum ether (bp 30–60°) with increasing proportions of ether] of the distillation pot residue led to isolation (11%) and characterization of **9a** by ir comparison with commercial material. Heating at 1:3 molar mixture of **9a**:Si_2Me_6 under the above reaction conditions afforded recovered **9a** in 90% yield, and a similar control study with **8a** led to quantitative recovery (vpc) of unchanged **8a**.

Repetition of the above experiment (42 hr of heating) with freshly distilled *o*-**nitrotoluene (7b)** yielded (vpc, column B, 100°, 60 ml/min) 22% unchanged nitro starting material and 14% **8b** which was identified by its vpc retention time. Column chromatography (same as with **7a**) led to isolation of a trace quantity (<5%) of unidentified dark red colored crystals (mp >300°) and pale yellow colored crystals which rapidly decomposed.

The above procedures were carried out with *p*-**nitrotoluene (7c)** using a 45-hr heating period. Quantitative vpc analysis revealed 50% **7c** and approximately 30% **8c**, which eluted as a peak extensively overlapped with a lesser amount of an unknown component having a slightly longer retention time; isolation of this later material was not successful. Column chromatography of the reaction mixture gave a yellow-colored oil which crystallized from petroleum ether (bp 30–60°) as light orange colored crystals (mp 140°) that were identified as the thermodynamically more stable[44] *trans*-**9c** azo product (10%, lit.[44] mp 144°; lit.[44] mp 105° for *cis*-**9c**).

Deoxygenation of Azoxybenzene with Si_2Me_6. A mixture of recrystallized azoxybenzene (99 mg, 0.5 mmol) and Si_2Me_6 (0.3 ml, 1.5 mmol) was subjected to the same reaction conditions as those reported above for **7a**. Tlc analyses [silica gel PF-254, petroleum ether (bp 30–60°)–ether (90:10)] indicated that very little (if any) azoxy compound remained and that a major product was accompanied by at least three minor, strongly fluorescent, slower eluting components. The major reduction product was isolated by thick-layer chromatography and was identified by ir comparison with authentic material as **9a** (36 mg, 40%).

Kinetics for Si_2Me_6 Deoxygenation of 7a. Three sealed ampoules containing aliquots of a stock solution of **7a** (0.25 mmol) in Si_2Me_6 (1 ml, 5 mmol) containing ODCB (0.05 mmol) as a vpc internal standard were heated in a constant temperature oil bath which was preset and maintained at 220 ± 3°. Tube removal after 4, 19, and 31 hr was followed by duplicate vpc measurements of relative values for [**7a**] given by (area **7a**)/(area ODCB). A value for $\tau_{1/2}$ = 33.8 hr ($k'_{220°}$ = 5.7 × 10^{-6} sec^{-1}) was obtained from a plot of ln ($[7a]_t/[7a]_i$) *vs.* time, which was linear and passed through the origin. A duplicate kinetic run gave $\tau_{1/2}$ = 34.7 hr ($k'_{220°}$ = 5.5 × 10^{-6} sec^{-1}). Use of the average psuedo-first-order deoxygenation rate constant ($k'_{220°}$ = 5.6 ± 0.1 × 10^{-6} sec^{-1}) in the Erying equation gave $\Delta G^{\ddagger}_{220°}$ = 41 kcal/mol.

Attempted Deoxygenation of 2-Nitrosobiphenyl (13). A solution of **13**[45] (0.17 *M*) and Si_2Me_6 (3.3 *M*) in ODCB was heated in the usual manner at 90° for 19 hr, as was a separate control sample of **13** (0.17 *M*) in ODCB. Tlc [silica gel PF-254, petroleum ether (bp 30–60°)–ether (90:10)] of both the reaction mixture and control sample gave essentially the same spectrum of components, which featured a spot having the same R_f value as **4** and indicated the presence of at least five additional components, plus residual "tars." Only a trace amount of **13** was apparently present and **3** was not detected. Thick-layer chromatographic (same conditions) isolation of the component initially thought to be **4** (mp 243°) gave a 10 w/w % yield of dark brown colored crystals (mp 148–151°) after crystallization from CH_2Cl_2–petroleum ether (bp 30–60°). Further characterization of this unknown product was not pursued, although it was found to have the same vpc retention time as authentic **4** (column D, 170°, 60 ml/min).

Deoxygenation of 1 with 6 in the Presence of CCl_4. A solution of **1** (1 *M*), **6** (2 *M*), and CCl_4 (4 *M*) in ODCB was heated in the usual manner at 240° for 1.5 hr. Quantitative vpc analysis (same as above, with triphenylmethane internal standard) indicated the presence of 33% unreacted **1** with 35% and 1% yields of **3** and **4**, respectively. Material loss of 32% was associated almost entirely with a reaction product that eluted shortly after **1** and could not be isolated in a pure state for further characterization. Heating **4** (0.04 mmol) and CCl_4 (0.22 mmol) in ODCB under the above reaction conditions led to an ~10% (vpc) loss of **4**, while a similar control experiment with **3** (0.05 mmol) and CCl_4 (0.22 mmol) led to an ~60% decrease in the concentration of **3**.

Pyrolysis of 14a in the Presence of 7a and Si_2Me_6. A 1:1:3 molar mixture of **14a**[25]:**7a**:Si_2Me_6 was simultaneously heated (23 hr, 240°) in the usual manner with a second tube containing a 1:3 molar mixture of **14a**:Si_2Me_6. Duplicate vpc analyses (column B, 170°, 120 ml/min) of each reaction mixture, using appropriate thermal conductivity correction factors, gave molar ratios of **8a/9a** = 1.3 and 3.7 for the three- and two-component mixtures, respectively. Heating a 1:3 molar mixture of **7a**:Si_2Me_6 under the above reaction conditions gave a value of **8a/9a** = 3.5, while a duplicate experiment with a 42-hr heating period gave a molar ratio for **8a/9a** = 2.5, which was more in accord with earlier data obtained with **7a** listed in Table III.

Attempted Photochemical Deoxygenations. Approximately 3-ml aliquots of a cyclohexane stock solution of **1** [0.05 *M*; λ_{max} (C_6H_{12}) 290 mμ (log ε 3.2)] which contained a fivefold molar excess of Si_2Me_6 and tetradecane as an internal vpc standard, were irradiated at 3000 Å in stoppered quartz tubes using a Rayonet photochemical reactor equipped with a "merri-go-round" apparatus. After 4 and 16 hr, vpc analyses (column B, 160°, 120 ml/min) revealed that the concentration of **1** decreased by ~5 and 20%, respectively, without detectable (vpc) formation of **3** or **4**. Repetition of the above experiments using solutions that did not contain Si_2Me_6 gave essentially the same results, within experimental error. Analogous data were obtained by use of 2537-Å light.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation, and the Catholic University of America for their partial support of this work. We also acknowledge the assistance of Ms. Maria Thomas in the preparation of our manuscript.

Registry No.-**1**, 86-00-0; **3**, 90-41-5; **4**, 86-74-8; **7a**, 98-95-3; **7b**, 88-72-2; **7c**, 99-99-0; *trans*-**9c**, 21650-54-4; **13**, 21711-71-7; **14a**, 53783-47-4; azoxybenzene, 495-48-7.

References and Notes

(1) ACS–PRF Undergraduate Research Participant, 1973–1974.
(2) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964), and original literature citations therein. See also R. A. Abramovitch and B. A. Davis, *J. Chem. Soc. C*, 119 (1968); C. Floriani and G. Fanchinetti, *J. Chem. Soc., Chem. Commun.*, 17 (1973); and E. Sappa and L. Milone, *J. Organometal. Chem.*, **61**, 383 (1973).
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(18) Although our present mechanistic understanding of disilane deoxygenations of nitro compounds is admittedly superficial (*vide infra*), we believe it reasonable to associate the sluggish reactivity of Si_2Ph_6 with extraordinary rate-retarding steric effects at some point along the reaction coordinate.
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(25) F. P. Tsui, T. M. Vogel, and G. Zon, *J. Amer. Chem. Soc.*, **96**, 7144 (1974).
(26) Analogous α-elimination of alkoxysilanes in systems which yield carbenes[27] (R_2C:) and silylenes[28] (R_2Si:) has been reported.
(27) W. H. Atwell, D. R. Weyenberg, and J. G. Uhlmann, *J. Amer. Chem. Soc.*, **91**, 2025 (1969); A. G. Brook and P. J. Dillon, *Can. J. Chem.*, **47**, 4347 (1969).
(28) W. H. Atwell and D. R. Weyenberg, *J. Amer. Chem. Soc.*, **90**, 3438 (1968); *J. Organometal. Chem.*, **5**, 594 (1966).
(29) Formation of azoxy compounds from reaction of aryl nitroso compounds with phosphorus reagents *via* addition of derived arylnitrenes to unreacted nitroso starting material has been discussed.[4b]
(30) A control reaction (see Experimental Section) demonstrated that azoxybenzene [PhN=N(O)Ph] undergoes complete reaction with a threefold molar excess of Si_2Me_6 at 240° to yield 9a.
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(32) T. M. Vogel and G. Zon, unpublished work.
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(34) A. G. Anastassiou *J. Amer. Chem. Soc.*, **89**, 3184 (1967).
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(36) H. A. Morrison in "The Chemistry of the Nitro and Nitroso Groups," Part 1, H. Feuer, Ed., Interscience, New York, N.Y., 1969, Chapter 4, and original literature citations therein.
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(38) Nmr spectra were recorded on a Varian A-60 spectrometer at ambient probe temperature, using *ca.* 10 v/v % solutions in deuteriochloroform and tetramethylsilane as an internal reference. Ir and uv measurements were carried out with Perkin-Elmer Model 137 and Cary Model 15 spectrometers, respectively. A Varian Aerograph Model 920 thermal conductivity gas chromatograph was used for vpc studies; quantitative measurements utilized either predetermined thermal conductivity correction factors or addition of authentic material with an internal reference. Vpc columns were made of standard 0.25 in. aluminum or stainless steel tubing and include column A = 6 ft, 15% Apiezon L on Chromosorb W, 60–80 mesh; column B = 3 ft, 5% SE-30 on Chromosorb G, 60–80 mesh; column C = 6 ft, 15% SE-30 on Chromosorb G, 60–80 mesh; column D = 5 ft, 3% SE-30 on Varaport 30, 100–120 mesh (Varian Aerograph). All melting point and boiling point data are uncorrected.
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(40) H. Sakurai, K. Tominaga, T. Watanabe, and M. Kumada, *Tetrahedron Lett.*, 5493 (1966).
(41) G. Schott and V. Bondybey, *Chem. Ber.*, **100**, 1773 (1967).
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Dihydrophenophosphazine Ring System[1]

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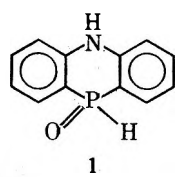
Received September 26, 1974

The reaction of diarylamines with phosphorus trichloride followed by treatment of the reaction mixtures with water has been employed to synthesize the secondary phosphine oxides **1**, **3**, **5**, and **7** and the spirophosphonium chlorides **2**, **4**, **6**, and **8**. A mechanism for the formation of the oxides has been proposed. Phosphinic acids have been prepared by oxidation of the oxides. The *N*-methyl derivative **12** has been obtained by a variant of the Friedel–Crafts reaction in which *N*-methyl-di-*p*-tolylamine and phosphorus trichloride were heated together in the presence of aluminum chloride and the reaction mixture was then hydrolyzed and oxidized.

It has long been known that the reaction of diphenylamine with phosphorus trichloride followed by treatment of the reaction mixture with water yields a heterocyclic phosphorus compound with the empirical formula $C_{12}H_{10}NOP$.[2] In 1960 Häring[3] published detailed directions for this reaction and showed that the heterocyclic compound is a secondary phosphine oxide, viz. 5,10-dihydrophenophosphazine 10-oxide (**1**). On attempting to repeat Häring's method of preparation, we found[4] that the phosphine oxide **1** was invariably admixed with a chlorine-containing compound $C_{24}H_{18}ClN_2P$. The chemical and spectral properties of the latter substance showed that it did not contain a P–H bond and that it was not a derivative of trivalent phosphorus. The structure of the unknown substance was unambiguously shown by an X-ray study[4,5] to be 10,10′(5*H*,5′*H*)-spirobiphenophosphazinium chloride (**2**). This was the first spirophosphonium compound re-



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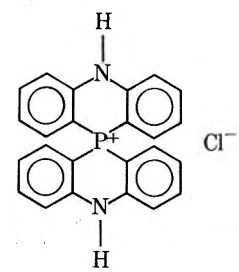

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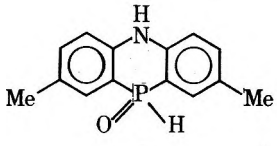
ported in which the phosphorus atom was a member of a ring that also contained nitrogen; it was, in fact, one of the relatively few spirophosphonium compounds known. The X-ray data showed that the C–N and C–P bond distances in this compound were unusually short and suggested that the central rings had aromatic character. A ^{31}P nmr study[5] also indicated that there was extensive electron delocalization in these rings. The ease of formation of the phosphine oxide 1 and the spirophosphonium compound 2, in addition to the inherent interest in such substances, has prompted us to investigate the reaction of phosphorus trichloride with diarylamines other than diphenylamine and to inquire into the mechanism of formation of the dihydrophenophosphazine ring system.

No special difficulties were encountered in preparing ring-substituted derivatives of 1 and 2. Thus, di-*p*-tolylamine yielded the phosphine oxide 3 and the spirophosphonium chloride 4; 4-methyldiphenylamine gave 5 and 6; and *N*-phenyl-1-naphthylamine gave 7 and 8. The phosphine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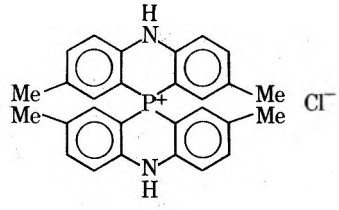
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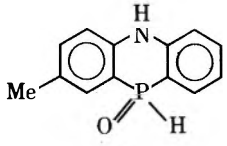
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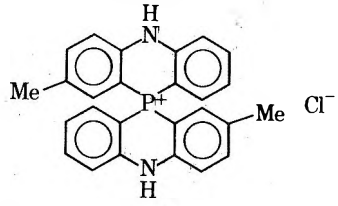
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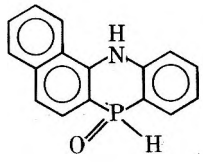
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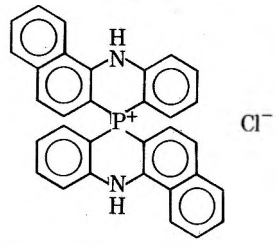
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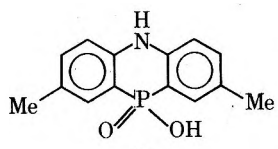
oxides 3, 5, and 7 were readily oxidized to the corresponding phosphinic acids 9, 10, and 11. It seems clear, therefore,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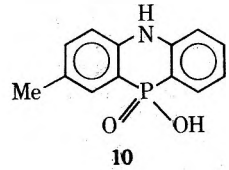
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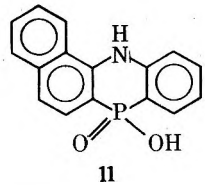
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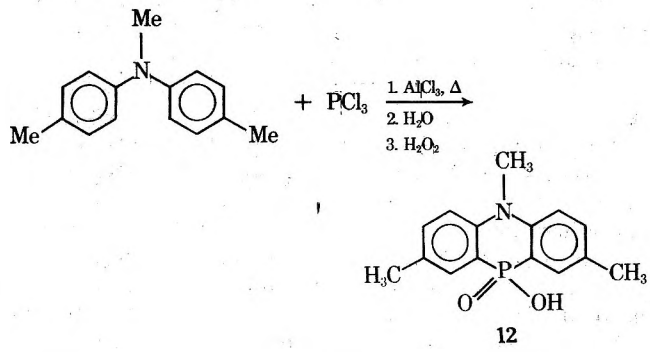
that a variety of dihydrophenophosphazine derivatives can be obtained *via* the interaction of diarylamines and phosphorus trichloride.

In contrast to the results discussed above, the reaction of *N*-methyldiphenylamine and phosphorus trichloride does not lead to the formation of heterocyclic derivatives of phosphorus. Thus, Michaelis and Schenk[2b] in 1890 reported that the aluminum chloride catalyzed condensation of *N*-methyldiphenylamine and phosphorus trichloride gives the phosphonous dichloride $PhN(Me)C_6H_4PCl_2$. Although the orientation of the dichlorophosphino group has apparently not been established, it has been generally assumed that the group enters para to the nitrogen.[6a] We have found that no reaction whatever occurred when a mixture of *N*-methyldi-*p*-tolylamine and phosphorus trichloride was refluxed for 12 hr.[7] In the presence of aluminum chloride, however, the ortho positions were attacked, and the *N*-methyl derivative 12 was obtained. This reaction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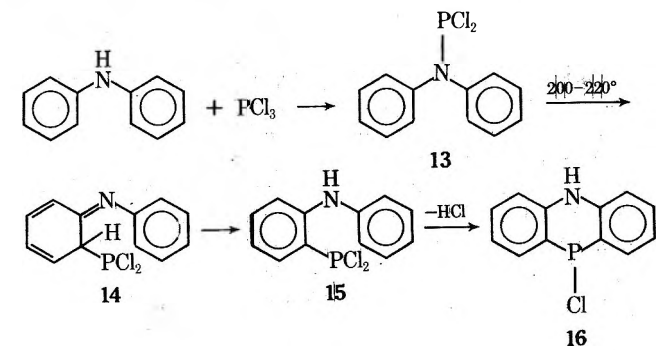
represents the first synthesis of an *N*-methylphenophosphazine derivative by the condensation of phosphorus trichloride and an aromatic amine.[8]

In the first edition of his monograph, Kosolapoff[9] suggested that the primary product of the interaction of diphenylamine and phosphorus trichloride is diphenylphosphoramidous dichloride, Ph_2NPCl_2 (13), which subsequently undergoes rearrangement and further condensation to yield a heterocyclic substance. We have prepared the dichloride 13 by the method of Sollott and Peterson[10] and have found that this compound at 200–220° does indeed rearrange and lose hydrogen chloride to give, after treatment with water, the same mixture of 1 and 2 obtained *via* the interaction of diphenylamine and phosphorus trichloride. The failure of the *N*-methyldiarylamines to react with phosphorus trichloride (except in the presence of aluminum chloride) would seem to be a consequence of the inability of these amines to form phosphoramidous dichlorides. The formation of the dihydrophenophosphazine ring by the interaction of diphenylamine and phosphorus trichloride appears to be consistent with the following sequence of reactions.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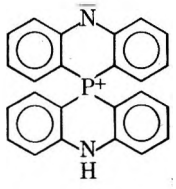
16

In the above mechanism, the rearrangement of 13 to 14 involves the transfer of the PCl_2 group to an ortho position and the formation of the type of intermediate usually postulated in electrophilic aromatic substitution. (Pearson and Buehler[11] have discussed other examples of enhanced ortho substitution in which the attacking reagent first forms a bond with the side chain and is then transferred to the aromatic ring.) Rearomatization of 14 accompanied by trans-

fer of aoton from carbon to nitrogen yields the phosphonous dichloride **15**, which would be expected[12] to readily undergo cyclodehydrohalogenation to give the phosphinous chloride **16**. And, finally, hydrolysis of **16** would certainly yield the phosphine oxide **1**.[13]

The aluminum chloride catalyzed interaction of the *N*-methyldiarylamines and phosphorus trichloride requires little comment, since the reaction of aromatic compounds with phosphorus trihalides under Friedel–Crafts conditions is well known.[6b] When the aromatic compound contains an alkyl, alkoxy, phenoxy, or halo substituent, the entering dihalophosphino group goes mainly para to the substituent already present. In the case of *p*-tolyl ether and *p*-tolyl sulfide (which, of course, have no available para positions), the phosphorus attacks positions ortho to the oxygen or sulfur and heterocyclic compounds are formed.[14] Thus, the reactions of the *N*-methyldiarylamines with phosphorus trichloride appear to be normal Friedel–Crafts reactions.

The most interesting and surprising finding noted in this investigation is the formation (albeit in low yields) of the spirophosphonium chlorides **2**, **4**, **6**, and **8**. Treatment of alcoholic solutions of these chlorides with aqueous sodium hydroxide yields fine yellow precipitates, which have not been purified since they are insoluble in water and the common organic solvents (except for glacial acetic acid, which apparently converts them to acetates). These yellow substances contain no chlorine, but their ir and mass spectra are virtually identical with the spectra of the corresponding chlorides, and they can be reconverted to the chlorides by treatment with hydrochloric acid. It seems likely that the yellow substances have zwitterionic structures like **17** and are resonance stabilized through canonical forms of type **18**.



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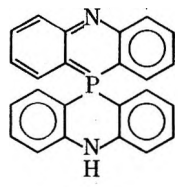

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Although the insolubility of the yellow substances discussed above has thus far prevented us from ascertaining their structures, we have made use of their properties in the isolation of both the phosphine oxides and the phosphonium chlorides from the mixtures obtained by the interaction of diarylamines and phosphorus trichloride. For example, when diphenylamine and phosphorus trichloride are allowed to a react by Häring's procedure[3] and the reaction mixture is treated with water, a solid is obtained which is soluble for the most part in cold 95% ethanol. Addition of aqueous sodium hydroxide to the ethanolic solution precipitated the yellow substance that could be converted to the phosphonium chloride **2**; the phosphine oxide **1** could then be isolated by evaporation of the filtrate from the yellow precipitate to a small volume. Adaptations of this technique were used in separating **3** from **4** and **5** from **6**. The separation of the naphthalene derivatives **7** and **8**, however, was more conveniently accomplished by column chromatography.

Molecular models[15] of the spirophosphonium chlorides **6** and **8** show that these molecules do not possess a plane of symmetry and are indeed chiral. Attempts to resolve these racemic mixtures are now in progress.

Experimental Section

Melting points were determined with a Mel-Temp capillary melting point apparatus and are uncorrected. Ir spectra were obtained with a Perkin-Elmer Model 521 spectrophotometer. Mass spectra were taken at 70 eV with an Associated Electrical Industries MS 12 recording mass spectrometer using a solid injection probe. Detailed fragmentation patterns deduced from metastable studies and accurate mass measurements will be published elsewhere. Elemental analyses on samples dried in vacuo at 140° were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

The reactions between phosphorus trichloride and the aromatic amines can be carried out in conventional round-bottom flasks equipped with a thermometer, magnetic stirrer, and reflux condenser protected with a drying tube. The reaction mixtures were, however, much more easily removed from similarly equipped "resin reaction kettles" (Fisher Scientific Co., Cat. No. 11-847). Performing the reactions in a atmosphere of dry nitrogen appeared to have no effect on the yields of the organophosphorus compounds.

5,10-Dihydrophenophosphazine 10-Oxide (1), 10,10′-(5*H*,5′*H*)-Spirobiphenophosphazinium Chloride (2), and 5,10-Dihydro-10-hydroxyphenophosphazine 10-Oxide. A mixture of diphenylamine (20 g, 0.12 mol) and PCl_3 (18 g, 0.13 mol) was stirred without heating for 2 hr, heated at 200–220° for at least 9 hr, and then treated cautiously with water as previously described.[3,5] The solid thus obtained was powdered and extracted with 300 ml of 95% ethanol. The resulting solution was filtered to remove about 1 g of an unidentified solid and then treated with 10% aqueous NaOH to precipitate a yellow substance believed to be 10,10′(5*H*)-spirobiphenophosphazine (**17** ↔ **18**). Treatment of this material with dilute hydrochloric acid yielded a slightly off-white solid, which on recrystallizaton from glacial acetic acid gave 8.2 g (8.3%) of analytically pure chloride **2**. Ir spectrum in Nujol exhibited N–H absorption at 3215 and 3125 cm^{-1} but no absorption near 2300 cm^{-1} characteristic of P–H stretching. The base peak of the mass spectrum was at *m/e* 364, which corresponds to a dehydrohalogenated derivative of **2**.

The basic ethanolic filtrate from the yellow substance **17** ↔ **18** was evaporated to about 75 ml and cooled, whereupon crude phosphine oxide **1** crystallized from solution. After recrystallization from glacial acetic acid, the yield of **1** was 6.2 g (24%): mp 214–216° (lit.[3] mp 214–216°); ir spectrum (Nujol) agreed well with that reported by Häring;[3] mass spectrum exhibited the molecular ion, *m/e* 215 (92%).

The original mother liquor from the crude **1** was evaporated to dryness, and the residue was oxidized by refluxing for 24 hr in a mixture of 40 ml of 95% ethanol and 60 ml of 4 *N* aqueous NaOH.[16] The crude phosphinic acid obtained by acidification of the resulting solution to Congo Red was recrystallized from 95% ethanol to yield 3.4 g (12%) of 5,10-dihydro-10-hydroxyphenophosphazine 10-oxide: mp 270–274° dec (lit.[3] mp 274–275°); ir spectrum (Nujol) in good agreement with Häring;[3] molecular ion, *m/e* 231, was the base peak of the mass spectrum.

2,2′,8,8′-Tetramethyl-10,10′(5*H*,5′*H*)-spirobiphenophosphazinium Chloride (4), 2,8-Dimethyl-5,10-dihydrophenophosphazine 10-Oxide (3), and 2,8-Dimethyl-10-hydroxy-5,10-dihydrophenophosphazine 10-Oxide (9). The reaction of di-*p*-tolylamine[17] (39.4 g, 0.21 mol) with PCl_3 (30.2 g, 0.22 mol) and the hydrolysis of the reaction mixture were carried out by the procedure described above. Extraction of the resulting solid with 400 ml of 95% ethanol at room temperature yielded a residue of 22.2 g, which was shown by its ir spectrum to consist mainly of the phosphine oxide **3**. This material could be purified or oxidized to the phosphinic acid **9**; the procedures used are described in the paragraphs below. Treatment of the ethanolic extract with 4 *N* aqueous NaOH gave a yellow precipitate, which was converted to a whitish solid by the addition of concentrated hydrochloric acid. Recrystallization from 95% ethanol gave 1.5 g (3%) of the phosphonium chloride **4**: mp >400°; base peak of the mass spectrum was *m/e* 420, corresponding to the loss of HCl.

Anal. Calcd for $C_{28}H_{26}ClN_2P$: C, 73.60; H, 5.74; Cl, 7.76; N, 6.13; P, 6.78. Found: C, 71.50; H, 6.07; Cl, 7.55; N, 6.10; P, 6.70.

Although the crude phosphine oxide mentioned above was only slightly soluble in 95% ethanol, it could be recrystallized from this solvent with the aid of a Soxhlet extraction apparatus. The yield of pure **3** was 30% (based on di-*p*-tolylamine), mp >400°, but sample turned yellow at about 245°: ir (KBr) 3260 and 3150 (NH), 2320 (PH), and 1150 cm^{-1} (P=O); mass spectrum exhibited the molecular ion, *m/e* 243 (90%).

Anal. Calcd for $C_{14}H_{14}NOP$: C, 69.13; H, 5.80; P, 12.73. Found: C, 69.33; H, 5.94; P, 12.74.

A 2.0-g sample of the crude phosphine oxide was oxidized by refluxing for 4 hr in a mixture of 30% H_2O_2 (20 ml), 4 *N* aqueous

NaOH (25 ml), 95% ethanol (15 ml), and water (100 ml). After the reaction mixture was cooled, a yellow precipitate was removed by filtration, treated with concentrated hydrochloric acid, and then recrystallized from 95% ethanol to yield 0.30 g (8%) of the phosphonium chloride **4**; thus, the total yield of **4** was 11%. Acidification of the filtrate from the yellow precipitate gave the crude phosphinic acid **9**, which was recrystallized from 95% ethanol: yield 1.5 g (33%); mp 289° dec; ir (KBr) 3180 (NH) and 1120 cm^{-1} (P=O); base peak of the mass spectrum was the molecular ion, *m/e* 259.

Anal. Calcd for $C_{14}H_{14}NO_2P$: C, 64.86; H, 5.44. Found: C, 64.85; H, 5.53.

2-Methyl-5,10-dihydrophenophosphazine 10-Oxide (5), 2,2'-Dimethyl-10,10'(5*H*,5'*H*)-spirobiphenophosphazinium Chloride (6), and 2-Methyl-10-hydroxy-5,10-dihydrophenophosphazine 10-Oxide (10). The reaction of 4-methyldiphenylamine[18] (8.2 g, 0.045 mol) with PCl_3 (6.2 g, 0.045 mol) and the subsequent hydrolysis were conducted by the same procedure used in the preparations above. Extraction of the resulting solid with 150 ml of 95% ethanol at room temperature yielded a residue, which was recrystallized from 95% ethanol to give 0.30 g (2%) of the oxide **5**: mp 205–206°; ir (KBr) 3250 and 3160 (NH), 2320 (PH), and 1155 cm^{-1} (P=O); the molecular ion, *m/e* 229 (95%), was prominent in the mass spectrum.

Anal. Calcd for $C_{13}H_{12}NOP$: C, 68.12; H, 5.28. Found: C, 68.38; H, 5.31.

The ethanolic extract mentioned above was treated with 4 *N* aqueous NaOH to yield a yellow precipitate, which was converted to the phosphonium chloride **6** by treatment with concentrated hydrochloric acid. After two recrystallizations from aqueous ethanol, the yield of pure **6** was 1.0 g (10%): decomposed at 270–280° with the evolution of a gas and finally melted with darkening at 375–385°; ir (Nujol) 3220 and 3130 cm^{-1} (NH); base peak of the mass spectrum was at *m/e* 392, corresponding to the loss of hydrogen chloride.

Anal. Calcd for $C_{26}H_{22}ClN_2P$: N, 6.53; P, 7.22. Found: N, 6.45; P, 7.19.

The filtrate from the yellow precipitate was evaporated to dryness, and the residue was oxidized by refluxing for 6 hr in a mixture of 30% H_2O_2 (25 ml), 4 *N* aqueous NaOH (30 ml), 95% ethanol (2 ml), and water (50 ml). The reaction mixture was filtered, the filtrate was acidified, and the precipitated phosphinic acid **10** recrystallized twice from MeOH. The yield was 2.7 g (25%): mp 270–272°; ir (Nujol) 3320 (OH), 3260 and 3170 (NH), and 1100 cm^{-1} (P=O); base peak of the mass spectrum was the molecular ion, *m/e* 245.

Anal. Calcd for $C_{13}H_{12}NO_2P$: C, 63.68; H, 4.93. Found: C, 63.90; H, 4.88.

7,12-Dihydrobenzo[*c*]phenophosphazine 7-Oxide (7), 7,7'(12*H*,12'*H*)-Spirobi[benzo[*c*]phenophosphazinium] Chloride (8), and 7-Hydroxy-7,12-dihydrobenzo[*c*]phenophosphazine 7-Oxide (11). The reaction of *N*-phenyl-1-naphthylamine[19] (43.8 g, 0.20 mol) with PCl_3 (27.5 g, 0.21 mol) was carried out and the reaction mixture was hydrolyzed as in the procedures above. The solid thus obtained weighed 50.0 g after being dried in vacuo. A 1.0-g sample of this material was dissolved in 30 ml of $CHCl_3$ and added to a column packed with 50 g of silicic acid (Bio-Sil A, 100–200 mesh) suspended in $CHCl_3$. The column was washed with 1 l. of $CHCl_3$, and 1 l. of 5% MeOH in $CHCl_3$ was then used as the eluent. The first band to separate was collected and proved to be the phosphine oxide **7**: yield, 0.40 g (36%); mp, after recrystallization from 95% ethanol, 238–240°; ir (KBr) 3280 and 3180 (NH), 2300 (PH), and 1160 cm^{-1} (P=O); base peak of the mass spectrum was the molecular ion, *m/e* 265.

Anal. Calcd for $C_{16}H_{12}NOP$: C, 72.45; H, 4.56; N, 5.28; P, 11.68. Found: C, 72.17; H, 4.57; N, 5.30; P, 11.36.

The second band that separated on the column yielded an oily material, which was not identified. Complete removal of the third band (which contained the phosphonium chloride **8**) from the column required 1 l. of 10% MeOH in $CHCl_3$: yield, 0.30 g (34%); mp, after recrystallization from 95% ethanol, >400°; ir (KBr) 3250 and 3160 cm^{-1} (NH); base peak of the mass spectrum was at *m/e* 464, corresponding to the loss of HCl.

Anal. Calcd for $C_{32}H_{22}ClN_2P$: C, 76.72; H, 4.43; N, 5.59; P, 6.18. Found: C, 76.43; H, 4.54; N, 5.82; P, 5.96.

A 5.0-g sample of the 50.0-g crude reaction product was oxidized by refluxing for 6 hr in a mixture of 30% H_2O_2 (30 ml), 4 *N* aqueous NaOH (20 ml), and water (100 ml). The reaction mixture was filtered, and the filtrate was acidified to precipitate the phosphinic acid **11**: yield 1.0 g (18%); mp, after recrystallization from glacial acetic acid, 290–295°; ir (KBr) 3220 and 3180 cm^{-1} (NH); base peak of the mass spectrum was the molecular ion, *m/e* 281.

Anal. Calcd for $C_{16}H_{12}NO_2P$: C, 68.33; H, 4.30. Found: C, 68.17; H, 4.32.

2,5,8-Trimethyl-10-hydroxy-5,10-dihydrophenophosphazine 10-Oxide (12). A mixture of *N*-methyl-di-*p*-tolylamine[20] (5.0 g, 0.024 mol), PCl_3 (6.5 g, 0.047 mol), and anhydrous $AlCl_3$ (1.3 g, 0.0098 mol) was stirred and refluxed for 24 hr. On pouring the reaction mixture over 200 g of cracked ice, a heavy oil was obtained, which solidified on standing. The solid was washed thoroughly with water, added to a mixture of 20% aqueous NaOH (50 ml) and 30% H_2O_2 (20 ml), and then heated at 100° for 1 hr. On cooling the resultant mixture, 2.2 g of a solid was obtained, which was removed by filtration and identified as unreacted *N*-methyldi-*p*-tolylamine. Acidification of the filtrate precipitated the phosphinic acid **12**, which was recrystallized from 95% ethanol: yield, 0.70 g (12%); mp 276–277°; pmr (CF_3CO_2H) τ 8.07 (s, 6, $ArCH_3$), 6.87 (s, 3, NCH_3), 3.04 (m, 6, aromatic H); ir (KBr) 1200–1150 cm^{-1} (P=O); base peak of the mass spectrum was the molecular ion, *m/e* 273.

Anal. Calcd for $C_{15}H_{16}NO_2P$: C, 65.93; H, 5.90. Found: C, 65.89; H, 5.96.

Acknowledgments. The authors wish to thank Dr. Kurt L. Loening for helping us name the heterocyclic compounds prepared and Dr. Saddik Shakshooki for performing some exploratory experiments.

Registry No.—**1**, 53778-28-2; **2**, 34283-79-9; **3**, 53778-29-3; **4**, 53778-30-6; **5**, 53778-31-7; **6**, 53778-32-8; **7**, 53798-59-6; **8**, 53778-33-9; **9**, 53798-60-0; **10**, 53798-61-1; **11**, 53798-62-2; **12**, 53798-63-3; 5,10-dihydro-10-hydroxyphenophosphazine 10-oxide, 53778-28-2; diphenylamine, 122-39-4; PCl_3, 7719-12-2; di-*p*-tolylamine, 620-93-9; 4-methyldiphenylamine, 620-84-8; *N*-phenyl-1-naphthylamine, 90-30-2; *N*-methyl-di-*p*-tolylamine, 3480-97-5.

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Applications of Artificial Intelligence for Chemical Inference. XIV.[1] A General Method for Predicting Molecular Ions in Mass Spectra

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Received August 2, 1974

A general method for predicting molecular ions is described which is effective whether or not the molecular ion peak is present in a mass spectrum. The method involves generating a set of fragment losses characteristic of a particular spectrum. These losses are then used to predict a ranked set of candidate molecular ions. The method is applicable to both high- and low-resolution spectra and has been successfully applied to a wide range of classes of compounds.

Assignment or identification of the molecular ion plays a key role in structural elucidation from mass spectral data. Knowledge of the molecular ion highly restricts the space of possible molecular structures which might have given rise to a particular spectrum and virtually all spectral interpretations—be they purely conceptual or automated—start with this datum. However, a problem that frequently arises is that a spectral peak corresponding to the molecular ion is absent from the spectrum. To proceed with an automated analysis when the molecular ion is unknown (may be present or absent), as is done with the Heuristic DENDRAL programs,[2,3] it is essential to make inferences as to possible molecular ion candidates before the analysis can proceed.

Several procedures for molecular ion inference have been proposed by McLafferty,[4] Biemann,[5] and Reed.[6] These methods have usually been applied to high-resolution spectra. Molecular ions are selected when a number of criteria are satisfied, *e.g.*, correct parity of mass and nitrogen atom content, correct isotopic distributions, and reasonable composition losses to other peaks in the spectrum. Generation of candidates beyond the highest mass present in the spectrum is done by addition of a set of "good losses" to the highest mass. In this paper we propose an alternative and more general method for molecular ion prediction.

The method we propose parallels the work of Biemann[5] and McLafferty[4] in that candidate molecular ions are accepted or rejected using a set of "bad losses." However, the procedure used here to infer candidate molecular ions does not depend on an arbitrary set of "atoms or groups which can be easily lost from the molecular ion."[5] Rather, a set of "secondary losses" (see below), derived solely from the spectrum being analyzed, is used to infer candidate molecular ions. In addition, we use an intensity index derived from the spectrum to rank our candidate molecular ions rather than the ratio of good losses to bad losses reported previously.[4]

In simplest terms the present method involves a search for all masses (or compositions) X, such that X either appears in the lower half of the spectrum or X is a difference (mass or composition) formed from any pair of ions in the spectrum. Members of this set that do not satisfy certain mass and/or composition constraints are excluded. The range of possible molecular ions then spans every ion which is the sum of an X (from above) and a peak in the upper half of the spectrum. Plausible molecular ions are then filtered from this latter set and ranked using the peak intensities in the upper half of the spectrum and a cumulative intensity index assigned to the X's. Details of these procedures are given below.

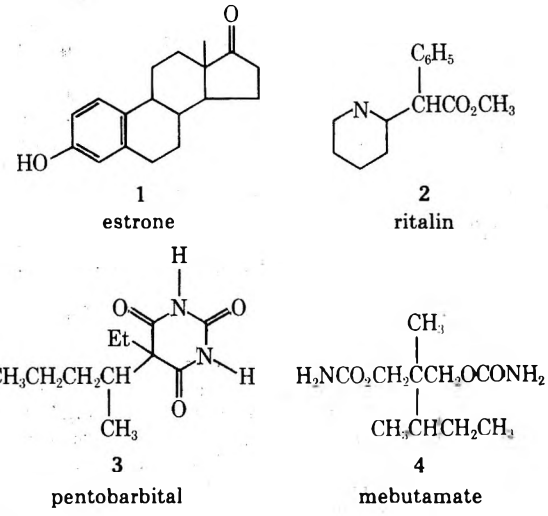
Basis of the Method

Crucial to the proposed method is the following postulate. *"There exists at least one SECONDARY LOSS in a spectrum that will match a PRIMARY LOSS from the molecular ion irrespective of whether the molecular ion is present in the spectrum."* A PRIMARY LOSS in this context is a composition or mass of a fragment that is lost from the molecular ion. In the spectrum shown in Figure 1 the loss of 55 amu (244 − 189) is an example of a primary loss. The complete set of primary losses for this spectrum is 55, 73, 100, 101, and 111. Additional losses such as 129 amu (244 − 115) are not considered because they exceed an upper loss limit that has been arbitrarily set in the program. Note that primary losses are not known to the program because the molecular ion is unknown.

A SECONDARY LOSS is any member of the union of the two sets of fragments defined below. One set consists of losses from all fragment ions other than any possible molecular ion candidate present in the spectrum. The other set is made up of the compositions or masses in the lower half of the spectrum. Referring to the spectrum in Figure 1 the loss of 18 amu (189 − 171) and the peak at mass 88 are examples of secondary losses.

The basic postulate can be restated as follows. For every mass spectrum there is a high probability that any mass or composition lost from the molecular ion will be also observed as a loss from one fragment ion to another or will itself appear as a fragment ion in the lower mass regions of the spectrum. Initial testing of this postulate has indicated that the secondary losses almost invariably contain at least one element of composition or mass which will combine with an element in the spectrum to give the correct molecular composition or mass, independently of the presence or absence of a peak corresponding to the molecular ion.

Chart I
Structures of Some Compounds Whose Molecular Ions Were Predicted



1 estrone

2 ritalin

3 pentobarbital

4 mebutamate

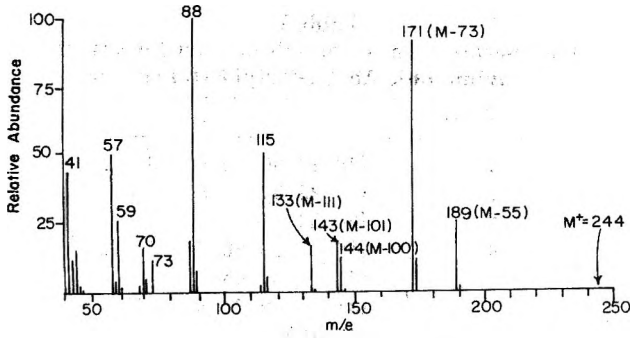


Figure 1. Mass spectrum of dimethylmalonic acid *n*-butyl ester.

An example given in Table I indicates the level of matching of primary losses by secondary losses in the high-resolution mass spectrum of estrone (1) (see Chart I). Each such matching is additional evidence for choice of the correct molecular ion. This is not an isolated example; a high degree of matching exists for most classes of compounds. We point out that some matchings for low-resolution data may be due to numerical accidents (*i.e.*, a difference of 17 mass units may correspond to either a comsitional difference of OH or NH_3). These accidents result in generation of bad candidates that would be rejected in a high-resolution analysis. Although, intuitively, it might seem that this method should generate excessive numbers of candidates, in practice simple evaluation heuristics reject most candidates.

Table I
Matching of Primary Losses by Secondary Losses for Estrone (1)

Primary losses[a] (from the molecular ion)	Other peaks showing identical losses[b]
C_1H_3	214 199 186
C_2H_4	214 199 186
C_2H_5	213
$C_2H_7O_1$	214 213 199
$C_3H_4O_1$	255 242 184
$C_3H_5O_1$	242 233
$C_4H_7O_1$	255 199 186
$C_4H_7O_1$	242
$C_5H_8O_1$	199
$C_5H_{10}O_1$	214 199
$C_4H_{11}O_2$	
$C_6H_8O_1$	255 241 187
$C_6H_9O_1$	242
$C_6H_{11}O_1$	214
$C_5H_{11}O_2$	
$C_5H_{12}O_2$	
$C_5H_{13}O_2$	
$C_7H_{10}O_1$	255

[a] Primary losses are from the molecular ion (270 $C_{18}H_{22}O_2$) of estrone (high-resolution spectrum). Column 2 lists other peaks in the spectrum showing the same losses. [b] Only nominal masses are shown; however, high-resolution masses and elemental compositions derived therefrom were used in the analysis.

Working from this postulate concerning primary and secondary losses it is a rather straightforward task to construct a method capable of generating a set of molecular ion candidates that will include the correct molecular ion in almost all instances. It is not necessary to use all secondary losses and the complete spectrum to obtain reliable molecular ion prediction. Details of the procedure presently used will now be outlined.

Method for Molecular Ion Inference

The proposed method for molecular ion prediction falls within the plan–generate–test paradigm common to many artificial intelligence applications, including Heuristic DENDRAL.[2,3] This strategy seems to be an efficient one for solving the present problem.

(A) Planning Phase. The basic function of the planning phase is to establish the appropriate set of secondary losses needed for the molecular ion generation phase. Initially the raw spectrum of mass-intensity pairs is approximately corrected for ^{13}C isotope contributions and then transformed into a list of "mass clusters" as dictated by the natural clustering of the spectral peaks. For our purposes a cluster is a group of peaks in which successive peaks are separated by less than three mass units. Before the clustering procedure is performed the spectrum is passed through a selective thresholding procedure which ensures that eventual clusters do not join because of the presence of ions which are low in abundance compared with the major ions in the local region of the spectrum. From each cluster the three most intense peaks are kept; the rest are discarded. Any peaks that are less than one-third the most intense peak in each cluster are also arbitrarily deleted to give a reduced spectrum. In this transformation relative intensity filtering is achieved without the exclusion of important low intensity peaks that may be present at the high mass end of a spectrum. For the dimethylmalonic acid butyl ester spectrum (Figure 1, molecular ion absent) the reduced low-resolution spectrum of mass–intensity pairs is (41, 44), (57, 48), (59, 23), (70, 15), (73, 12), (88, 100), (115, 46), (133, 14), (143, 18), (144, 16), (171, 95), (189, 26).

Before actually generating the secondary loss set a number of consistency checks are made to determine whether there are any molecular ion candidates present in the spectrum. This is done by checking to see if there are no "bad losses" (see Tables II and III) to neighboring clusters, and if there is a peak in the top cluster of the appropriate parity with respect to the nitrogen content flag (set after the series analysis phase, below). Note that the entries in Table III are selected at the discretion of the user. In esence any molecular ion candidate present in the spectrum must pass the same tests as described below for generated molecular ion candidates. Also, for high-resolution data, any nonsense compositions resulting from numerical accidents are filtered out. In the case of dimethylmalonic acid *n*-butyl ester (Figure 1) the dominant odd mass series 57, 73, 115, 143, 171 (components differ by multiples of 14 or CH_2) together with the greater number of odd than even peaks in the reduced spectrum indicate firstly that there is not an odd

Table II
Bad Compositions Used by the Secondary Loss Generation Phase and the Candidate Filter

Composition	Bad losses
$C_xH_yO_zN_n$	$x < 0$ or $y < 0$ or $z < 0$[a] or $n < 0$[a]
C_x	$x > 0$ $y = 0$ $z = 0$ $n = 0$
H_y	$x = 0$ $y > 2$ $z = 0$ $n = 0$
O_z	$x = 0$ $y = 0$ $z > 0$ $n = 0$
N_n	$x = 0$ $y = 0$ $z = 0$ $n > 0$
H_yO_z	$x = 0$ $z > y$ or $y > 2z$
$C_xH_yO_zN_n$	$x \neq 0$ $y > (2x + 3)$
$C_xH_yO_zN_n$	$x \neq 0$ $z > (x + 1)$
$C_xH_yO_zN_n$	$x \neq 0$ $y \neq 0$ $x > y + 1$

[a] The negative restriction is necessary to exclude losses where the mass difference is valid but the composition difference has negative components.

Table III
Bad and Poor Losses Used by the Secondary Loss Generation Phase and the Candidate Filter

Bad Losses[a]											
4	5	6	7	8	9	10	11	12	13	21	22	23
24	25	26	37	38	50	51	52	53	65	66		
Poor First Losses												
19	39	40	54	62	64	67	68	70	82			
83	84	86	88	89	90	91	92	93	94	95		
96	98	99	103	104	105	107	108	109	110			

[a] Bad losses are taken to be those that can almost always be rejected on chemical grounds. Poor losses are generally of low probability but cannot be excluded on chemical grounds.

Table IV
Secondary Losses from Peak Clusters in Dimethylmalonic Acid *n*-Butyl Ester (Figure 1)

Peak cluster	Loss set
189	(18 45 56 74 101)
171	(27 28 56 83 98 101 112 114)
144 and 143	(29 56 71 74 85 103 28 55 70 73 84 86 102)
133	(18 45 60 63 74 76 92)
115	(27 42 45 56 58 74)
88	(15 18 29 31 47)
73 and 70	(14 16 32 29)
59 and 57	(18 16)

number of nitrogens present and also that there is no molecular ion peak.

The secondary losses are generated by exhaustive application of the following procedure to the reduced spectrum. Successive mass and/or composition "inter-cluster" losses are generated for all ions in all clusters of the reduced spectrum. The secondary losses from all clusters in the dimethylmalonic acid *n*-butyl ester spectrum are shown in Table IV. As the losses are calculated impossible composition differences, if one is examining a high-resolution mass spectrum (*e.g.*, a loss of two carbons with a gain of six hydrogens), and bad mass differences (*e.g.*, the loss of 10 mass units generated from masses 143 and 133 in our example) are rejected (see Tables II and III). Other restrictions that have arbitrarily been placed on the losses are that they are limited in magnitude to less than 115 mass units and even if they pass this restriction they cannot be greater than approximately half the largest mass observed in the spectrum. These losses (excluding those from any possible molecular ion candidate) are combined with the list of fragment masses in the lower half of the spectrum. The resulting set is the secondary loss set referred to previously. In some instances this set may contain more than 50 entries. The secondary loss set for the dimethylmalonic acid *n*-butyl ester example (Figure 1) is 14, 15, 16, 18, 27, 28, 29, 31, 32, 41, 42, 45, 46, 47, 55, 56, 57, 58, 59, 60, 63, 70, 71, 73, 74, 76, 83, 84, 85, 86, 87, 88, 92, 101, 102, 103, 112, 114.

At this stage in the procedure two approaches are available, each with certain advantages. If one wishes to avoid using all the secondary losses to generate molecular ion candidates a set of loss series can be formed. The criterion for establishing a loss series is that elements of the series differ in composition multiples of CH_2 or, in the case of low-resolution data, there exist differences that are multiples of 14. The complete set of loss series for dimethylmalonic acid *n*-butyl ester generated from its secondary loss set is given in Table V. To obtain a restricted set of secondary losses for molecular ion prediction one can choose to use

Table V
Loss Series Formed from Secondary Losses for Dimethylmalonic Acid *n*-Butyl Ester (Figure 1)

Loss series no.	Series list
1	(28 42 56 70 84 98 112)
2	(15 29 57 71 85)
3	(58 86 114)
4	(18 32 46 60 74 88 102)
5	(27 41 55 83)
6	(31 45 59 73 87 101)
7	(47 103)

Table VI
Ranked Candidate Molecular Ions for Dimethylmalonic Acid *n*-Butyl Ester (Figure 1)

Candidate	Ranking index
244	100
258	52
246	51
190	37

only the lower members (say the first two or three) of each loss series for molecular ion generation.

If instead of using a restricted set of secondary losses one chooses to use the complete set a likelihood ranking can be given to each of the molecular ion candidates. Details of the method used are given in the discussion of the filtering phase which follows the section on molecular ion generation below.

With the chosen set of secondary losses in hand the program switches to a generative mode.

(B) Molecular Ion Generation. Three main pieces of information are passed from the planning mode to the molecular ion generation mode. They are the chosen set of secondary losses, a list of the compositions or masses in the upper half of the reduced spectrum, and an indication as to whether there is an odd number of nitrogens present in the molecular ion (see above discussion of planning phase).

To generate the molecular ion candidates each member of the secondary loss list is added to each member of the upper half of the reduced spectrum of the appropriate parity. In our example (Figure 1) for dimethylmalonic acid *n*-butyl ester the secondary loss "55" when added to 133, 143, 171, and 189 gives candidates with masses of 198, 226, and 244. Candidates generated that have a molecular weight or composition less than the ion at highest mass (excluding any impurity peaks that have been detected) are immediately excluded. The program copes with impurity peaks at the high mass end in high-resolution spectra by checking the compositions of losses from each of the peaks in the top three clusters against the "bad compositions" listed in Tables II and III. Any impurity peaks that are detected by accurate mass measurements are removed from the spectrum. No attempt is made to detect impurity peaks in low-resolution spectra.

(C) Filtering and Ranking of Molecular Ion Candidates. The filtering or testing part of the method performs three main functions. It uses a list of bad losses (Table III) and compositions (Table II) to reject some of the generated molecular ion candidates. Those candidates rejected in the dimethylmalonic acid *n*-butyl ester example are 198, 200, 220, 202, 212, 236, 226, 248, and 252. For instance the candidate 198 shows a loss of 9 amu (198 − 189) and so is unacceptable. The remaining molecular ion candidates are separated into a probable list and an unlikely list. To perform this latter operation each candidate is tested against two

Table VII
Sample Set of Results Showing Molecular Ion Prediction and Ranking

Compound	Mol formula	Highest mass present	Fragment missing[a]	Mol wt	Ranked at no.[b]
Ritalin (2)	$C_{14}H_{19}NO_2$	172 (M − 61)	$C_2H_5O_2$	233	4
Pentobarbital (3)	$C_{11}H_{18}N_2O_4$	197 (M − 29)	C_2H_5	226	2
Mebutamate (4)	$C_{10}H_{20}N_2O_4$	175 (M − 57)	C_4H_9	232	3
Tridecan-7-one	$C_{13}H_{26}O$	155 (M − 43)	C_3H_7	198	4
Succinic acid methyl ester	$C_6H_{10}O_4$	116 (M − 30)	CH_2O	146	2
Caprylic acid methyl ester	$C_9H_{18}O_2$	129 (M − 29)	C_2H_5	158	3
Glutaric acid methyl ester	$C_7H_{12}O_4$	129 (M − 31)	CH_3O	160	1
Maleic acid butyl ester	$C_{12}H_{20}O_4$	173 (M − 55)	C_4H_7	228	2
N-TFA α-alanine[c] butyl ester	$C_9H_{14}NO_3F_3$	186 (M − 55)	C_4H_7	241	2
N-TFA norleucine butyl ester	$C_{12}H_{20}NO_3F_3$	227 (M − 56)	C_4H_8	283	2
N-TFA valine butyl ester	$C_{11}H_{18}NO_3F_3$	227 (M − 42)	C_3H_6	269	2
N-TFA threonine butyl ester	$C_{12}H_{15}NO_5F_6$	323 (M − 44)	C_3H_8	367	1
N-TFA phenylalanine butyl ester	$C_{15}H_{18}NO_3F_3$	216 (M − 101)	$C_5H_9O_2$	317	4
n-Undecyl alcohol	$C_{11}H_{24}O$	154 (M − 18)	H_2O	172	1
4-Methyloctan-4-ol	$C_9H_{20}O$	129 (M − 15)	CH_3	144	1

[a] These fragment composition losses from the molecular ion are only postulated. Their validity could only be confirmed by high-resolution studies. [b] Note "ranked at number 1" is the program's best choice for a molecular ion candidate. [c] TFA refers to the trifluoroacetyl derivative.

"poor loss" lists. The first set contains a list of poor first losses (Table III) extending up to 115. A first loss is the smallest loss from a candidate molecular ion (*e.g.*, 55 amu for mol wt 244 in Figure 1). The second set of poor losses is a subset of the first set. Losses from each generated ion to every ion in the top three clusters of the spectrum are compared with this second set of losses. If a loss generated from a molecular ion candidate is found to be present in either of these poor loss lists it is given an unlikely ranking; otherwise it is placed on the list of probable molecular ion candidates. The following candidates were given an unlikely ranking for our ester example: 216, 218, 228, 230, 234, 292, and 274. We find that 216 is rejected because it shows a loss of 27 amu (Tables II and III) to the peak at 189, for example.

Following through our example for dimethylmalonic acid *n*-butyl ester, we find that of the three candidates (198, 226, 244) generated by the secondary loss 55, only 244 is not rejected by the filter. A loss of 9 is shown by 198 and a loss of 37 is shown by 226—both of which have been deemed unacceptable losses.

If the option has been invoked to use all secondary losses (including even losses minus one hydrogen or one mass unit, *e.g.*, if 88 is in the even list 87 is included in the odd list) the probable molecular ion candidates are ranked. Peak intensities are used to obtain this ranking. First, a cumulative intensity measure is found for each secondary loss. This is done by taking the sum of the average intensities for each pair of peaks involved in each secondary loss transition. A reduced weight is assigned to the losses 14, 28, etc. Intensities of peaks in the lower half of the spectrum are also added to any secondary losses with which they correspond. Then by adding in the intensities of peaks in the upper half of the spectrum that generate a given molecular ion candidate it is possible to obtain a likelihood rating for each candidate. In the complete analysis for dimethylmalonic acid *n*-butyl ester (Figure 1) the top four candidates and their associated ratings were as shown in Table VI. The correct molecular ion 244 gets the highest ranking (100). Inspection of the losses from each cluster gives an explanation for this. Losses from 189, 171, 144, 143, 133, and 115 include 55, 56, 73, 74, and 101 a number of times, and since these losses match those from the molecular ion (244) they will make a high contribution to the ranking for the candidate 244. This ranking method is particularly effective when the molecular ion is present, as might be expected because of the high degree of matching of primary losses by secondary losses. It also works well for cases where the molecular ion is absent from the spectrum. Details of ranking performance are given in Tables VII and VIII.

Details of the Computer Program

To cope efficiently with the data manipulations required, the method for molecular ion prediction has been implemented in the list processing language LISP[7] (versions exist in LISP 1.5 and INTERLISP). The symbolic and list processing capabilities are highly desirable when working with the composition lists of high-resolution mass spectra.

The program has been structured to find molecular ions in either a high- or low-resolution mass spectrum. With

Table VIII
A Summary of Ranking Results Is Given for Various Classes of Compounds Tested

Class	Mol ion in top 3	Mol ion in top 5	Total no. of compds
Amines	62	67	68
Alcohols[a]	51	54	57
Ketones	42	44	44
Ethers	33	34	34
Acetals	13	14	14
Amino acid derivatives	9	11	13
Thioethers	11	12	12
Drug compounds	6	8	9
Methyl esters	6	8	8
Butyl esters	4	5	6

[a] Program failed to generate the correct candidate for one alcohol, *tert*-butyl alcohol.

low-resolution spectra the program is given a list of mass–intensity pairs. High-resolution data are accepted as a list of mass–intensity–composition triplets. No other parameterization is necessary. However, changes to the filter set and other parameters can easily be made.

On a normal low-resolution run the program takes between 1 and 4 sec of CPU time on an IBM 360/67 to produce the list of molecular ion candidates. High-resolution determinations which always involve considerable manipulation of composition lists may take from 30 to 60 sec.

Results and Discussion

Referring to the results for dimethylmalonic acid *n*-butyl ester it can be seen that the primary losses (−55), (−73), and (−101) are matched by secondary losses. Closer inspection of the molecular structure for this ester reveals the link between the losses and structural components, *e.g.*, –COOBu has a mass of 101 and –OBu has a mass of 73. The loss of 55 may correspond to the structural unit C_4H_7.

To test the validity and performance of the method for molecular ion prediction, spectra from a wide variety of classes of compounds have been tested, particularly for low-resolution data. The only high-resolution spectra tried have been estrogens, pregnanes, and progesterones most of which show molecular ions.

Among the low-resolution spectra tested (Tables VII and VIII) were derivatized amino acids, barbiturates, and other drug compounds, aliphatic esters, acetals, alcohols, amines, ethers, and ketones, many of which have no molecular ions.

The results tabulated in Tables VII and VIII give some idea of the effectiveness of the program for molecular ion prediction. When the molecular ion is present as for most amines and ketones, and some ethers and alcohols, the program almost always predicts it as the most likely candidate or at least in the top three ranked candidates. It should be emphasized that this high ranking is purely on the basis of the cumulative intensity index and that the same high ranking would have been obtained even if the molecular ions had been removed from the spectra.

For the derivatized amino acids, aliphatic esters, and barbiturates which do not show molecular ions, performance in prediction was still good. Ranking usually placed the correct candidate within the top five of those predicted. Sometimes when (M − 73) is the highest mass, ranking is poor. This may be due to the decreasing stability of fragments with increasing mass. Alcohols and acetals which quite often show (M − 1) or (M − 15) ions rather than a molecular ion are effectively handled by the program. Results so far indicate that there is a high probability (greater than 95% for 250 spectra of more than 10 classes) that the molecular ion will be in the top five candidates, a workable number for a computer program employed in molecular structure analysis. Of the 250 spectra tested 100 did not show significant molecular ions.

It should be emphasized that the present method for molecular ion prediction has been developed primarily as part of a larger program devoted to the computer interpretation of mass spectra. It is offered as a method for determining molecular ions in routine, conventional electron impact mass spectra, when methods such as chemical ionization and field ionization are not available or applicable.

Limitations of the Program

The method as stated in its most general form can cope with most molecular ion prediction problems. However, by working from a reduced spectrum and by not using all secondary losses an error in prediction may occasionally occur. Also an unusual loss currently on the list of bad losses (*e.g.*, 4 amu) may cause rejection of the correct molecular ion candidate.

The program as presently written may have problems with low-resolution spectra containing more than one chlorine or bromine because of heavy isotope contributions. Impurity peaks at high mass in low-resolution gc–mass spectral runs will also cause problems. Furthermore, if the largest mass peak in the spectrum is less than half the molecular weight (M) or there is a peak at say (M − 101) at highest mass for low M the program will fail. The unusual problems in which the program may fail are likely to be the same problems with which the chemist will have considerable difficulty if given no additional information.

Acknowledgments. One of us (R.G.D.) gratefully acknowledges the support of a CSIRO Postdoctoral Studentship. We are indebted to Dr. Alan Duffield for supplying many of the test spectra. We would also like to thank Dr. N. Sridharan for his comments. This work was supported by a grant (No. RR-612-05A1) from the National Institutes of Health.

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Metathesis of 1-Hexene and Cyclooctene[1]

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Received August 28, 1974

The metathesis reaction between 1-hexene and cyclooctene was examined using several catalysts derived from WCl_6 and an organometallic compound. Using preferred catalysts, $WCl_6 \cdot EtOH/EtAlCl_2$ or $WCl_6 \cdot 2Et_2O/Bu_4Sn$, a high percentage of cyclooctene (>70%) was consumed in a few hours. The reaction product consisted of linear nonconjugated polyenes belonging to three different homologous series. The principal component in the reaction product was $C_{14}H_{26}$ (1,9-tetradecadiene) resulting from the cross-metathesis of 1-hexene and cyclooctene. Ethylene and 5-decene, formed by the self-metathesis of 1-hexene, underwent cross-metathesis with cyclooctene to produce $C_{10}H_{18}$ (1,9-decadiene) and $C_{18}H_{34}$ (5,13-octadecadiene). Further reaction of these primary cross-metathesis products with cyclooctene gave higher members of the homologous series. The influence of the nature of the catalyst, 1-hexene/cyclooctene molar ratio, and cyclooctene conversion on component distribution in the reaction product was determined.

Olefin metathesis is a transition metal catalyzed reaction involving the reorganization of bonds of olefins *via* transalkylidenation.[2,3] It has been investigated primarily for the polymerization of cycloolefins into polyalkenamers. Both heterogeneous[4] and homogeneous[5] catalysts have been found useful in promoting this reaction. Potential applications of the olefin metathesis reaction have been recently reviewed.[5-7]

The cross-metathesis reaction between an α-olefin and a cycloolefin or cyclodiene has been reported in the literature.[8-11] Hérisson and Chauvin[12] and Kelly[13] independently found that the product from the reaction of 1-pentene and cyclopentene consists primarily of linear nonconjugated polyenes having one terminal double bond per molecule. Porri and coworkers[14] have studied the reaction of norbornene with 1-pentene using catalysts derived from iridium. In all these studies, the reaction products were examined after low conversions of reactants (1–15%). In this paper, we have quantitatively characterized the reaction product resulting from the cross-metathesis of 1-hexene and cyclooctene. Experimental conditions were chosen to give cyclooctene conversions of 70% or greater. Several catalysts derived from WCl_6 and an organometallic compound were employed for the study.

Results and Discussion

$WCl_6 \cdot EtOH/EtAlCl_2$ Catalyst.[2] A chromatogram of the reaction product from the cross-metathesis of 1-hexene and cyclooctene using the $WCl_6 \cdot EtOH/EtAlCl_2$ catalyst is shown in Figure 1. In order to characterize the various components in the mixture, seven fractions corresponding to the glc peaks were isolated by the preparative glc unit and analyzed by mass spectrum, nmr, and ir. The results are summarized in Table I.

Fractions 1, 2, and 3 comprising 7, 8.5, and 40 wt % of the product, respectively, were assigned (mass spectral data) the molecular formulas $C_{10}H_{18}$, $C_{10}H_{20}$, and $C_{14}H_{26}$, respectively, and correspond to the following structures:

fraction 1, 1,9-decadiene, $CH_2{=}CH(CH_2)_6CH{=}CH_2$

fraction 2, 5-decene, $C_4H_9CH{=}CHC_4H_9$

fraction 3, 1,9-tetradecadiene, $CH_2{=}CH(CH_2)_6CH{=}CHC_4H_9$

Fraction 4 (12.5 wt % of product) was found to contain primarily two compounds having the molecular formulas $C_{18}H_{32}$ and $C_{18}H_{34}$ (mass spectral data). These compounds were present in molar proportions of 40 and 60% (glc). Based on the chemistry of the metathesis reaction, they were assigned the structures $CH_2{=}[CH(CH_2)_6CH{=}]_2CH_2$ and $C_4H_9CH{=}CH(CH_2)_6CH{=}CHC_4H_9$, respectively.

Fractions 5, 6, and 7 represented 14.5, 7, and 5.5 wt % of the product, respectively. The various compounds presented therein belonged to the following three different homologous series of which $C_{10}H_{18}$ in fraction 1, $C_{14}H_{26}$ in fraction 3, and $C_{18}H_{34}$ in fraction 4 were first members.

Series A: the main peaks are assigned to $C_{14}H_{26}$, $C_{22}H_{40}$, and $C_{30}H_{54}$ components of the unsymmetric homologous series $CH_2{=}[CH(CH_2)_6CH{=}]_nCHC_4H_9$ representing about 60 wt % of the total product (primarily $C_{14}H_{26}$).

Series B: composed of $C_{18}H_{34}$, $C_{26}H_{48}$, and $C_{34}H_{62}$ of the symmetric homologous series $C_4H_9CH{=}[CH(CH_2)_6CH{=}]_nCHC_4H_9$ representing about 13% of the product.

Series C: contained $C_{10}H_{18}$, $C_{18}H_{32}$, $C_{26}H_{46}$, and $C_{34}H_{60}$ of the symmetric homologous series $CH_2{=}[CH(CH_2)_6CH{=}]_nCH_2$ representing about 14% of the product.

In the above series, n is an integer and its smallest value is 1. All compounds belonging to the series A, B, and C must contain moieties derived from both the reactants. Consequently, 5-decene (fraction 2) is not included in series B. Likewise, ethylene is not included in series C.

The relative molar ratio of the first components of series A, B, and C, namely, $C_{14}H_{26}$, $C_{18}H_{34}$, and $C_{10}H_{18}$, respectively, containing one cyclooctene-derived octenamer unit and constituting a triad, was approximately 4:1:1. The components of the next triad containing two octenamer units were also present in a similar ratio. However, Hérisson, *et al.*,[12] reported triad ratios of 10:1:1 to 20:1:1 for the reaction of cyclooctene with propylene or 1-pentene in chlorobenzene with a $WOCl_4/(C_4H_9)_4Sn$ catalyst. The relatively high proportion of series A components reported in the latter study is presumably a consequence of the reaction conditions and low cyclooctene conversions (1–15%). Under our experimental conditions, cyclooctene conversion was 70% or greater. Apparently, the cross-metathesis reaction leading to series A components prevails at low cycloolefin conversion but competing reactions leading to series B and C components become important as cyclooctene is depleted. A simplified reaction scheme is given in Scheme I. In addition, series A components may get converted to series B and series C components by subsequent metathesis reaction.[15]

It should be noted that peaks corresponding to macrocyclic oligomers $C_{16}H_{28}$ and $C_{24}H_{42}$, which are reported[16] to be formed during the ring opening polymerization of cyclooctene, are not seen by mass spectrum in the metathesis reaction product. However, $C_{32}H_{56}$ (tetramer) was observed in trace amounts in fraction 6. The absence of $C_{16}H_{28}$ and $C_{24}H_{42}$ does not necessarily preclude their formation in small amounts and subsequent reaction with one of the α-olefins present. The formation of $C_{32}H_{56}$ in trace

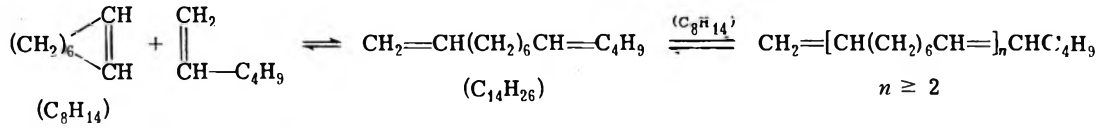
Table I
Characterization of the Metathesis Product[a] of 1-Hexene and Cyclooctene (WCl_6·EtOH/$EtAlCl_2$ Catalyst)

Glc		Mass spectrum			
Fraction no.[b]	Wt % of components	Parent mass obsd (m/e)[c]	Mol formula assigned	Nmr Anal	Series[d]
1	7	138.1393*	$C_{10}H_{18}$	2 terminal double bonds	C
2	8.5	140.1554*	$C_{10}H_{20}$	1 internal double bond	
3	40[e]	194.2029*	$C_{14}H_{26}$	1 terminal and 1 internal double bonds	A
4	12.5[f]	250.2648* 248	$C_{18}H_{34}$ $C_{18}H_{32}$	Consistent with 60 mol % $C_{18}H_{34}$ and 40 mol % $C_{18}H_{32}$	B and C
5	14.5[g]	304.3118*	$C_{22}H_{40}$	1 terminal and 2 internal double bonds	A
6	7	360.3749* 358	$C_{26}H_{48}$ $C_{26}H_{46}$	Consistent with 80 mol % $C_{26}H_{48}$ and 20 mol % $C_{26}H_{46}$	B and C
7	5.5[h]	414.4244* 440 468[i] 470	$C_{30}H_{54}$ $C_{32}H_{56}$ (trace) $C_{34}H_{60}$ $C_{34}H_{62}$		A, B, and C (except $C_{32}H_{56}$)

[a] Reaction conditions were the same as shown for Figure 1. [b] Fraction numbers refer to those in the chromatogram (Figure 1). All fractions were 98–99.5% pure, except fraction 1 (95% pure) and fraction 4 (81% pure). [c] Mass numbers with asterisks represent major peaks by high resolution mass spectrometry. [d] Homologous series refer to those in Scheme I. [e] $n^{30}D$ 1.4430; the internal double bond had 45% cis and 55% trans (ir). [f] $C_{18}H_{34}/C_{18}H_{32}$ molar ratio = 1.50 (glc analysis using a 20-ft, 20% UC-W98 on 60–80 mesh Chromosorb W column). [g] $n^{30}D$ 1.4622; 60% cis and 40% trans double bonds (ir). [h] 93% of C_{30} and 6% of C_{34}. For calculations, 3% each of $C_{34}H_{60}$ and $C_{34}H_{62}$ was assumed to be present (glc analysis using column in footnote *f*). [i] Mass peak was not observed (possibly due to side reactions?).

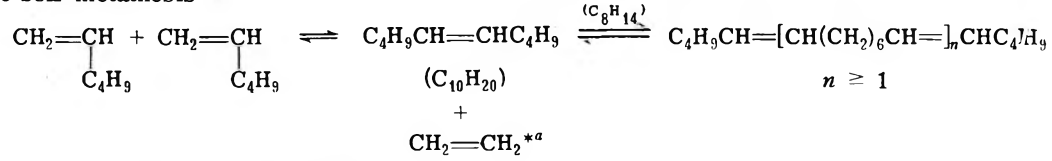
Scheme I
Schematic Diagram for Metathesis of Cyclooctene and 1-Hexene

Hexene–cyclooctene cross-metathesis



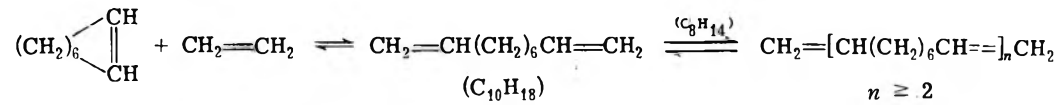
Series A

Hexene self-metathesis



Series B

Ethylene–cyclooctene cross-metathesis



Series C

[a] The presence of ethylene was ascertained by glc on a 50-ft di-*n*-decyl phthalate column.

amounts might result from the intramolecular cyclization of the diterminal polyene $C_{34}H_{60}$ (series C; $n = 4$) by pinching off ethylene.

The effect of reaction time on the distribution of components in series A, B and C is shown in Figure 2 using the $WCl_6 \cdot C_2H_5OH/EtAlCl_2$ catalyst. Cyclooctene consumption was increased to 86 wt % from 70% as the reaction time was increased to 24 hr from 0.25 hr. Concurrently, there was a slight decrease in the weight percentage of series A components as a consequence of an increase in the weight percentages of both series B and series C components. If the metathesis product were to be utilized for copolymerization with an α-olefin to produce an unsaturated copolymer, it is desirable to terminate the metathesis reaction after 30 min since increase in the relative amount of series C components at longer reaction times will increase gel content of the copolymer.

Catalyst systems based on Et_3Al or $(i\text{-}Bu)_3Al$ with $WCl_6 \cdot EtOH$ exhibited low activity for the metathesis reaction between 1-hexene and cyclooctene. They gave cy-

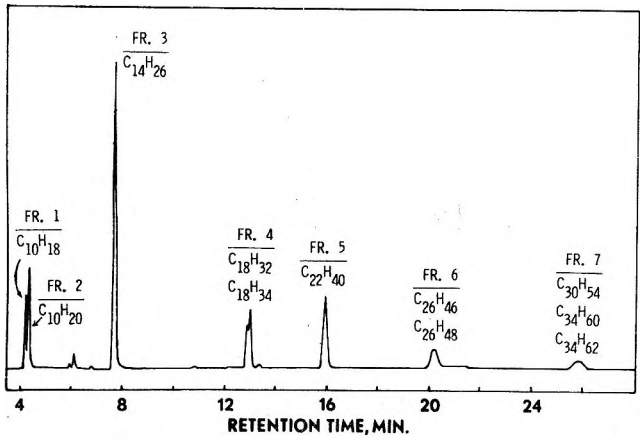


Figure 1. Chromatogram of the reaction product in the metathesis reaction of cyclooctene and 1-hexene. Conditions: catalyst, $WCl_6 \cdot EtOH/EtAlCl_2$; Al/W/O atomic ratio = 4:1:1; 1-hexene/cyclooctene molar ratio = 2; cyclooctene/WCl_6 molar ratio = 1300; reaction for 30 min at 25°.

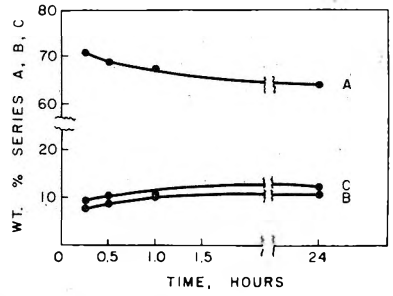


Figure 2. Effect of reaction time on product distribution in the metathesis reaction of cyclooctene and 1-hexene using $WCl_6 \cdot EtOH/EtAlCl_2$ catalyst. Conditions: same as in Figure 1.

clooctene conversion of about 5% in 24 hr, with only one peak ($C_{14}H_{26}$) detectable by glc.

$WCl_6 \cdot CF_3CH_2OH/EtAlCl_2$ Catalyst. The distribution of components in the three series is shown in Figure 3 for the $WCl_6 \cdot CF_3CH_2OH/EtAlCl_2$ catalyst. Cyclooctene conversion of 91 to 96% was obtained, with only slight changes in the product distribution, as the reaction time was increased from 0.25 to 24 hr. In calculating the product distribution here, the relative proportions of components corresponding to fractions 1 and 2 as well as the relative distribution of components in fractions 4, 6, and 7 were assumed to be the same as in Table i. This catalyst gave 44, 13, and 18 wt % of series A, B, and C components, respectively, compared to 60, 13, and 14% resulting from the C_2H_5OH-modified catalyst. Thus, the $WCl_6 \cdot C_2H_5OH/EtAlCl_2$ catalyst gives a higher proportion of the polymerizable components, together with a markedly improved ratio of series A/series C components. The data in Figures 2 and 3 indicate that the two catalyst systems appear to be essentially dead after about 1 hr.

$WCl_6 \cdot 2Et_2O$/Organotin Catalysts.[17] Several catalysts prepared from $WCl_6 \cdot 2Et_2O$ and organotin compounds were examined for the metathesis reaction between 1-hexene and cyclooctene. The reaction conditions were similar to those employed with $WCl_6 \cdot$ alcohol/$EtAlCl_2$ catalysts (Figures 2 and 3). As shown in Table II, only Bu_4Sn and $(C_6H_5)_4Sn$ gave catalysts having fairly high activity. The catalysts based on organotin compounds having one or two chlorine atoms gave less than 5% cyclooctene conversion under these conditions.

Glc of the metathesis product from the tin/tungsten-catalyzed reaction of 1-hexene and cyclooctene indicated that

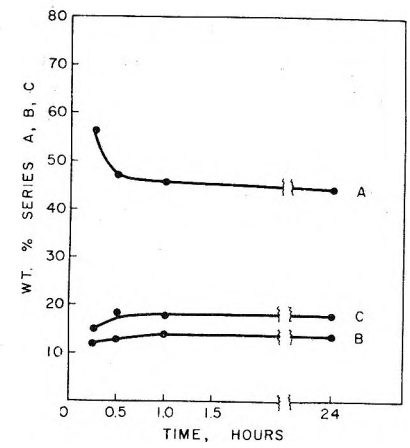


Figure 3. Effect of reaction time on product distribution in the metathesis reaction of cyclooctene and 1-hexene using $WCl_6 \cdot CF_3CH_2OH/EtAlCl_2$ catalyst. Conditions: same as in Figure 1.

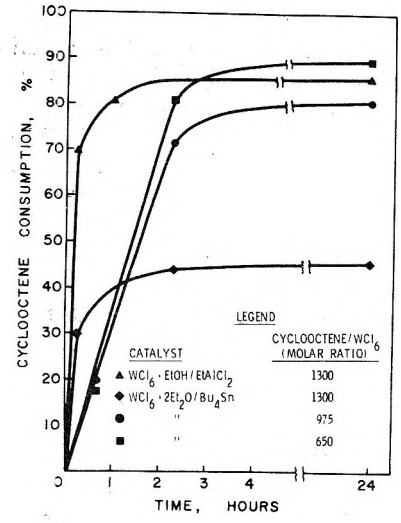


Figure 4. Effect of reaction time on cyclooctene consumption in the metathesis reaction of cyclooctene and 1-hexene. Conditions: for catalyst $WCl_6 \cdot EtOH/EtAlCl_2$, Al/W/O atomic ratio = 4:1:1; for catalyst $WCl_6 \cdot 2Et_2O/Bu_4Sn$, Sn/W/O atomic ratio = 2:1:2; 1-hexene/cyclooctene molar ratio = 2; 25°.

the various compounds present also belonged to the three homologous series described earlier. The $WCl_6 \cdot 2Et_2O/Bu_4Sn$ catalyst was examined at three different catalyst levels for the metathesis of 1-hexene and cyclooctene and the results compared with those obtained by using $WCl_6 \cdot EtOH/EtAlCl_2$ (Figure 4). The rate of cyclooctene consumption with the tin catalyst is seen to be substantially slower (37% in 1 hr and 45% in 3 hr) than that obtained with the aluminum catalyst (~80% in 1 hr) at a cyclooctene/WCl_6 molar ratio of 1300. However, raising the catalyst level by 33 and 100% increased cyclooctene consumption to about 76 and 85%, respectively, in 3 hr.

The compositions of the metathesis products for the aluminum- and tin-catalyzed reactions from Figure 4 are compared in Figure 5. For this purpose, the effect of reaction time on the distribution of polymerizable (series A + C) and nonpolymerizable (series B) components is examined. The weight percentages of the three series were normalized to 100%. Both the tin- and aluminum-based catalysts give essentially identical distribution of components when compared at cyclooctene/WCl_6 molar ratio of 1300. At this catalyst level, the product consists of approximately 86–88% series A + C components and 14–12% series B components at the end of 3 hr. Upon increasing the $WCl_6 \cdot 2Et_2O/$

Table II
Metathesis of 1-Hexene and Cyclooctene using $WCl_6 \cdot 2Et_2O$/Organotin Compound Catalysts[a]

Tin compd	Sn/W (atomic ratio)	Cyclooctene consumption, % 2 hr	24 hr
Bu_4Sn	2	80–85	90
Bu_3SnCl	2	5	5
Bu_2SnCl_2	2	5	5
$(C_6H_5)_4Sn$	2	5	37[b]
	4	43[b]	47[b]
$(C_6H_5)_3SnCl$	2	5	5

[a] 1-Hexene/Cyclooctene molar ratio 2.0; cyclooctene/WCl_6 molar ratio 650; benzene/cyclooctene vol ratio 3; reaction at 25°; *n*-octane used as the internal standard. [b] These reaction products had essentially the same component distribution as that obtained with the Bu_4Sn catalyst at equivalent conversion of cyclooctene.

Table III
Effect of 1-Hexene/Cyclooctene Molar Ratio on the Composition[a] of Metathesis Product ($WCl_6 \cdot 2Et_2O/Bu_4Sn$ Catalyst[b])

Component of metathesis product	Wt % Hexene/Cyclooctene molar ratio 0.5	1.0	2.0
$C_{10}H_{18}$	9.7	10.2	14.2
$C_{10}H_{20}$	10.5	14.3	18.5
$C_{14}H_{26}$	18.7	20.2	29.6
$C_{22}H_{40}$	15.7	14.6	10.2
Cyclooctene consumed, %	95	95	88

[a] Cyclooctene/WCl_6 molar ratio = 1300; benzene/cyclooctene vol ratio = 3; reaction at 25° for 2 hr; *n*-octane used as the internal standard. [b] Sn/W atomic ratio = 2.

Bu_4Sn level 33 to 100%, the percentage of polymerizable components decreased slightly to 79% with a corresponding increase in nonpolymerizable components to 21%. There was essentially no change in the distribution when the reaction was allowed to continue for 24 hr and cyclooctene consumption increased by 10%. It should be noted that at the higher levels of the tin catalyst, the amount of 5-decene based on the total product increased from about 10 to 14% compared to 7% with the aluminum system.

Figures 4 and 5 show that the $WCl_6 \cdot 2Et_2O/Bu_4Sn$ system requires a somewhat higher catalyst level than the aluminum system for obtaining in high conversion a polyene product with a high percentage of polymerizable components. This catalyst system, in marked contrast to the $WCl_6 \cdot EtOH/EtAlCl_2$ system, gives easily reproducible results. Scale-up of the metathesis reaction between 1-hexene and cyclooctene in a 1-gallon container gave a product having essentially the same component distribution as obtainable in a 4-oz bottle.

Effect of 1-Hexene/Cyclooctene Molar Ratio. In the previous discussion, the molar ratio of 1-hexene/cyclooctene for the W/Al and W/Sn catalyst systems was kept at 2 in carrying out the metathesis reactions. This ratio was selected because our preliminary work with the W/Al catalyst system had shown that the relative amount of series A components was highest at this ratio without any sacrifice in the high conversion of cyclooctene to the polyene mixture. The effect of hexene/cyclooctene molar ratio on the

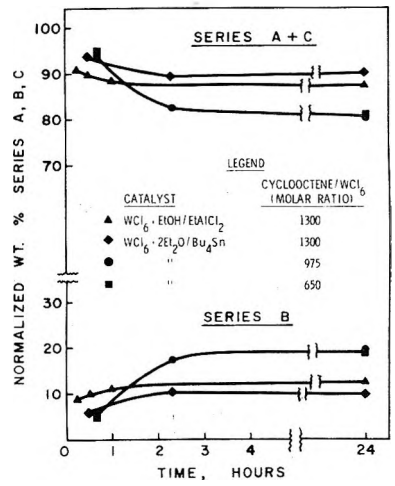


Figure 5. Effect of reaction time on product distribution in the metathesis reaction of cyclooctene and 1-hexene. Conditions: same as in Figure 4.

distribution of components in the $WCl_6 \cdot 2Et_2O/Bu_4Sn$ catalyzed metathesis product is shown in Table III. To simplify comparison, only the weight percentages of $C_{14}H_{26}$ and $C_{22}H_{40}$ of series A (peaks 3 and 5), $C_{10}H_{20}$ (peak 2) and $C_{10}H_{18}$ (peak 1) of series C were determined from the chromatograms since peaks for these components were well-defined. The overall conversion of cyclooctene to products is reasonably similar for all three ratios. However, the ratio 2 is preferred for the formation of $C_{14}H_{26}$, $C_{10}H_{20}$, and $C_{10}H_{18}$. The enhanced formation of $C_{10}H_{20}$ at this ratio is due to the greater availability of 1-hexene for undergoing self-metathesis. The greater availability of cyclooctene at the lower ratios contributes to enhancement in the formation of $C_{22}H_{40}$ at the expense of $C_{14}H_{26}$ by the cross-metathesis reaction between $C_{14}H_{26}$ and cyclooctene. Similarly, the areas of peaks 4 and 6 increased relative to the combined area of peaks 1 and 2 at the lower ratios (data not shown), consistent with the increased cross-metathesis of cyclooctene with $C_{10}H_{18}$ and $C_{10}H_{20}$.

Experimental Section

Monomers and Solvent. High purity 1-hexene (Gulf) and benzene (Fischer) were dried by passing through an 18-in. activated-silica column and stored over molecular sieves (Linde 4A-XW). Cyclooctene (Cities Service) was distilled over calcium hydride or passed through a silica–alumina column prior to use.

Catalysts. Solutions of $EtAlCl_2$ (1.55 *M*), organometallic tin compounds (0.1–0.2 *M*), and WCl_6 (0.05 *M*) were prepared in benzene under nitrogen. Solutions of WCl_6 were modified by adding appropriate amounts of an alcohol or diethyl ether. In the case of $(C_6H_5)_4Sn$, a 0.20 molar suspension in benzene was used.

Monomers and solvents of high purity and freshly modified WCl_6 solutions were found to be essential for obtaining reproducible results.

Metathesis Reaction. The experimental conditions were organometallic/WCl_6 molar ratio = 2–4; cyclooctene/WCl_6 molar ratio = 650–1300; hexene/cyclooctene molar ratio = 0.5–2; benzene/cyclooctene volume ratio = 3. The order of addition was solution of reactants, organometallic compound, WCl_6 modified with ether or an alcohol. In a typical experiment, the metathesis reaction mixture for characterization studies was prepared in a 1-qt bottle fitted with a metal cap having perforations and backed with a self-sealing gasket and Teflon linear. A solution of 0.50 mol of cyclooctene, 1.0 mol of hexene, 200 ml of benzene, and 10 ml of *n*-octane (glc internal standard) was sparged with nitrogen for three minutes. The catalyst components, 0.75 ml of $EtAlCl_2$ and 8.0 ml of $WCl_6 \cdot EtOH$ solutions, were added by syringe into the reactants solution and the bottle was capped under nitrogen. After agitation on a mechanical shaker for 30 min (ambient temperature, 25°), glc analysis of the homogeneous reaction mixture indicated a 94% con-

sumption of cyclooctene. The reaction was terminated at this point with 1 ml of methanol. The resulting mixture was concentrated on a roto-evaporator under aspirator vacuum to remove benzene, hexene, and cyclooctene prior to fractionation by preparative glc.

Analytical Procedures. Analysis by glc was routinely performed on a Hewlett-Packard 7620A Model gas chromatograph using a 6 ft × ⅛ in. 10% UC-W98 on 80–100 mesh Diatoport S column, programmed from 80 to 270° in 20 min.

As stated earlier, a typical metathesis product was concentrated by the removal of benzene, hexene, and cyclooctene. The concentrate was fractionated by means of a Hewlett-Packard preparative gas chromatograph unit and seven fractions were isolated. They were analyzed by nmr, ir, and mass spectrum.

Nmr analyses were carried out on a Varian A60 spectrometer and ir spectra recorded on a Perkin-Elmer Model 21 spectrophotometer. High resolution mass spectrum measurements were made on a Du Pont Model 21-110C mass spectrometer using perfluorokerosene as the reference compound.

Acknowledgment. The authors are grateful to R. A. Hively and R. E. Hinton for glc fractionation, Dr. T. L. Folk for mass spectroscopy, Dr. H. Y. Chen and B. A. Sibbio for nmr, J. K. Clark and R. A. Scott for ir, and D. K. Romain for technical assistance.

Registry No.—1-Hexene, 592-41-6; cyclooctene, 931-88-4; WCl_6, 13283-01-7; $EtOH/EtAlCl_2$, 53777-80-3; $CF_3CH_2OH/EtAlCl_2$, 53777-81-4; $2Et_2O/Bu_4Sn$, 53777-82-5; $2Et_2O/Bu_3SnCl$, 53777-83-6; $2Et_2O/Bu_2SnCl_2$, 53777-84-7; $2Et_2O/(C_6H_5)_4Sn$, 53777-85-8; $2Et_2O/(C_6H_5)_3SnCl$, 53777-86-9.

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Synthesis of Fatty Acids Using Organocopper(I) Ate Complexes Derived from Grignard Reagents[1]

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Received August 13, 1974

Fatty acid esters have been synthesized in good yield by reaction between copper(I) ate complexes formed from methylcopper(I) and primary or secondary Grignard reagents and esters of primary iodoalkylcarboxylic acids. The synthetic method is illustrated with procedures for $CH_2{=}CH(CH_2)_{19}CO_2C_2H_5$, $C_6H_5CH_2O(CH_2)_{16}CO_2C_2H_5$, $CH_3(CH_2)_{25}CO_2C_2H_5$, $CH_3O_2C(CH_2)_{22}CO_2CH_3$, $C_2H_5O_2C(CH_2)_{32}CO_2C_2H_5$, and $CH_3(CH_2)_4CH(CH_3)(CH_2)_{10}CO_2CH_3$. The reaction sequence uses starting Grignard reagent with high efficiency, provides product mixtures that are conveniently worked up, and tolerates a variety of functional groups. It provides the most direct route presently available to a variety of representative classes of simple fatty acids.

A number of procedures for the synthesis of fatty acids are available.[3] Those most commonly used for fatty acids not containing extensive unsaturation include the reaction of carbonyl compounds with alkylidene phosphoranes,[4] the Kolbe anodic coupling of half esters of dicarboxylic acids,[5] and the acylation of enamines with acid chlorides followed by hydrolysis of the resulting β-diketones and Wolff–Kishner reduction of the product keto acid.[6]

The reaction of carbonyl compounds with alkylidene phosphoranes is particularly useful for the preparation of diastereomerically pure unsaturated fatty acids, and has also been used in the preparation of branched-chain fatty acids. Its deficiencies are that it often involves multiple steps of only moderate yields and requires a difficult separation of products from triphenylphosphine oxide. Kolbe electrolysis of half esters of dicarboxylic acids is a useful route to symmetrical long-chain dicarboxylic acid esters, but is not applicable to the preparation of unsymmetrical compounds. The procedure developed by Hünig and coworkers is applicable to the synthesis of asymmetrically disubstituted fatty acids, symmetrically disubstituted fatty acids, and both straight- and branched-chain fatty acids. Although versatile, it is lengthy.

We have developed an efficient alternative to these procedures based on carbon–carbon bond formation by selective coupling between one alkyl group of a "mixed" copper(I) ate complex and primary iodoalkyl carboxylic esters.[7] This procedure is compatible with a number of functional groups, yields products cleanly and in high yield, and is applicable to a number of representative classes of fatty acids.

Results

Both primary and secondary Grignard reagents react with methylcopper(I) and form copper(I) ate complexes that selectively transfer the alkyl group originally bonded to magnesium in high yield in alkylation reactions. By using the readily available methyl or ethyl 11-iodoundecanoate in this reaction, it is possible to synthesize a variety of fatty acids. A typical procedure—that for ethyl 21-do-

Table I
Fatty Acid Esters Synthesized from Grignard Reagents Using Organocopper(I) Ate Complexes "R_1CH_3CuMgX" and Esters of 11-Iodoundecanoic Acid

Grignard reagent (R_1)	Registry no.	Scale, mmol	Product	Isolated yield, %[a]
$CH_2{=}CH(CH_2)_9MgCl$	53808-81-4	100	$CH_2{=}CH(CH_2)_{19}CO_2C_2H_5$	79
$C_6H_5CH_2O(CH_2)_6MgCl$	53835-11-3	200	$C_6H_5CH_2O(CH_2)_{16}CO_2C_2H_5$	64
$CH_3(CH_2)_{15}MgBr$	53808-83-6	50	$CH_3(CH_2)_{25}CO_2C_2H_5$	87
$BrMg(CH_2)_{12}MgBr$	53862-77-4	25	$H_5C_2O_2C(CH_2)_{32}CO_2C_2H_5$	85
$BrMg(CH_2)_{12}MgBr$		50	$CH_3O_2C(CH_2)_{22}CO_2CH_3$[b]	72
$CH_3(CH_2)_4CH(CH_3)MgBr$	53808-85-8	100	$CH_3(CH_2)_4CH(CH_3)(CH_2)_{10}CO_2CH_3$	54

[a] These yields are based on the Grignard reagent. A 20% excess of the 11-iodoundecanoic acid ester was used. [b] Methyl 6-iodohexanoate was used as alkylating agent.

Scheme I
Reaction of Methyl (10-Undecenyl)cuprate with Ethyl 11-Iodoundecanoate to Yield Ethyl 21-Docoseneoate

$$CH_2{=}CH(CH_2)_8CH_2Cl \xrightarrow[2.\ CH_3Cu(I)]{1.\ Mg,\ THF} \text{"}CH_2{=}CH(CH_2)_8CH_2Cu^-CH_3MgCl^+\text{"} \xrightarrow[THF,\ 79\%]{I(CH_2)_{10}CO_2Et} CH_2{=}CH(CH_2)_{19}CO_2Et$$

cosenoate—is outlined in Scheme I. Reaction of undec-10-enylmagnesium chloride with methylcopper(I) generated a mixed copper(I) ate complex. This complex in turn reacted with ethyl 11-iodoundecanoate (0.12 mol) selectively by transfer of the undec-10-enyl moiety; ethyl 21-docosenoate was isolated in 79% yield.

This procedure is generally applicable (Table I): either primary or secondary Grignard reagents can be used; the starting Grignard reagent may contain certain functional groups (ethers or olefins); the alkylating agent may incorporate the full range of functional groups stable in cuprate coupling reactions (ethers, olefins, esters, ketones); α,ω-di-Grignard reagents[8] can be used to prepare esters of long-chain dicarboxylic acids.

This method for the preparation of fatty acid esters has a number of advantages over previously described methods: the reaction involves only one coupling step and is shorter than the enamine method developed by Hünig and coworkers; products are obtained in high yield and can be isolated easily; starting materials are in general readily available; specialized electrochemical apparatus is unnecessary.

We have briefly investigated mixed alkyl(alkynyl)cuprates in these coupling reactions and found them to be unsatisfactory (Table II). Alkyl(alkynyl)cuprates prepared from organo*lithium* reagents have been effectively used in the selective transfer of an alkyl group in alkylation reactions;[7,9] however, these procedures apparently do not work well with Grignard reagent derived cuprates. Table II also indicates that although alkyl bromides do give acceptable yields, alkyl iodides are significantly better substrates. Mixed ate complexes containing copper(I) derivatives of mercaptans[10] and alkyl tosylates[11] have both proved useful in carbon–carbon bond-forming reactions based on organolithium reagents; we have not explored either in these organomagnesium-based reactions. The basis for the selectivity in the transfer of the Grignard reagent derived alkyl group in these procedures is not well understood. Indeed, the basis for selectivity in transfer of alkyl groups from mixed diorganocuprates is in general only qualitatively understood.[7,9,10] Regardless of the origin of the selectivity for transfer of the larger alkyl group in these cuprates, this selectivity serves usefully to permit efficient use of the alkyl groups originally present in the Grignard component of the reaction mixture.

Table II
Yields in Selective Transfer of Grignard Reagent Derived Alkyl Groups from Copper(I) Ate Complexes "$R_1R_2CuMgCl$" in Alkylations with Alkyl Halides

R_1[a]	R_2[b]	RX	Yield, % R_1R
$CH_2{=}CH(CH_2)_8CH_2-$	$(CH_3)_3CC{\equiv}C-$	$C_5H_{11}Br$	23 (15)[c]
	$(CH_3)_3CC{\equiv}C-$	$C_5H_{11}I$[d]	55
	$(CH_3)_3CC{\equiv}C-$	$C_5H_{11}I$[e]	60
	Me	$C_5H_{11}Br$	71[f]
	Me	$C_5H_{11}I$	92

[a] This alkyl group was derived from an alkylmagnesium chloride. [b] This alkyl group was derived from an alkyllithium reagent. [c] Lower yields resulted when the alkylcopper was prepared first and then allowed to react with 2,2-dimethylbutynyllithium. [d] A 50% excess of pentyl iodide was used. [e] A 500% excess of pentyl iodide was used. [f] This yield was obtained after stirring the reaction mixture for 3 hr at room temperature (see Experimental Section). Yields obtained just after the reaction mixture had warmed to room temperature were 5–10% lower.

Conclusion

The alkylation of alkyl(methyl)copper(I) ate complexes, in which the alkyl group is derived from a Grignard reagent, with iodo-substituted carboxylic acid esters forms the basis for a facile synthesis of a variety of substituted and unsubstituted fatty acids. This reaction proceeds with high selectivity in transfer of the alkyl group and gives products that can be conveniently isolated in high yield by recrystallization. This reaction is particularly well suited for the synthesis of α,ω-disubstituted fatty acid esters. It also affords a convenient route to branched- and straight-chain fatty acid esters. Further, these procedures illustrate a procedure by which the alkyl group of a Grignard reagent can be selectively and efficiently transferred from mixed diorganocuprates in alkylation reactions.

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.[12] Diethyl ether was distilled from calcium hydride under nitrogen; 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 obtained 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 in sodium chloride cavity cells using a Perkin-Elmer Model 337 grating spectrometer. F & M Model gas chromatographs were used for GLC analyses. Mass spectra were taken on a RMU-6E Hitachi Perkin-Elmer mass spectrometer. Lithium re-

agents were purchased from the Foote Mineral Co. or Alfa Inorganics, Inc. Lithium reagents were analyzed by the Gilman double titration method.[13] 1-Chloro-6-hydroxyhexane, 3,3-dimethylbutene, 1,12-dibromododecane, 11-bromoundecanoic acid, and 10-undecenoic acid were obtained from the Aldrich Chemical Co. Less expensive technical grade 11-bromoundecanoic acid can also be used after distillation or purification by recrystallization from methanol or petroleum ether. 10-Undecenol and 10-undecenal were obtained from either International Flavors and Fragrances, Inc., Givaudan Corp., or California Aromatics and Flavors Inc. 1-Bromohexadecane was obtained from Air Products and Chemicals.

11-Chloroundecene. Following the procedure of Hooz and Gilani,[14] 10-undecenol (128 g, 0.75 mol) was allowed to react with tri-*n*-butylphosphine (152 g, 0.75 mol) in 500 ml of carbon tetrachloride to give 130 g (92%) of 11-chloroundecene: bp 78–79° (0.9 Torr) [lit.[15] bp 111–111.3° (10 Torr)]; ir (CCl_4) 1639 cm^{-1}; NMR ($CDCl_3$) δ 5.5–6.2 (m, 1 H), 4.75–5.2 (m, 2 H), 3.47 (t, 2 H), and 1.1–2.2 (m, 16 H). This reaction can be conveniently monitored by watching the disappearance of the hydroxyl peak in the ir. If necessary, the addition of more tri-*n*-butylphosphine will drive the reaction to completion after heating to reflux.

Ethyl 11-Iodoundecanoate. To an acetone solution of 11-bromoundecanoic acid (100 g, 377 mmol) was added sodium iodide (130 g, 872 mmol). This reaction mixture was then refluxed for 12 hr. After cooling to room temperature, the reaction mixture was poured into 3 l. of water. A solid formed which was separated by filtration and recrystallized from 500 ml of absolute methanol to give 114 g of pure 11-iodoundecanoic acid, mp 64–65° (lit.[16] mp 64–65°). Esterification with 200 ml of absolute ethanol in 200 ml of toluene containing 2 ml of sulfuric acid according to literature procedures[17] yielded ethyl 11-iodoundecanoate (88%): bp 149–151° (1 Torr) [lit.[18] bp 110–112° (0.15 Torr)]; ir (neat) 1740 cm^{-1}; NMR (neat) δ 4.07 (q, 2 H), 3.18 (t, 2 H), 2.2 (t, 2 H), 2.0–1.0 (m, 19 H). The methyl ester of 11-iodoundecanoic acid could also be prepared using a literature procedure with absolute methanol and sulfuric acid.[19] Methyl 11-iodoundecanoate thus prepared (78% yield) had bp 98–102° (0.15 Torr); ir (CCl_4) 1741 cm^{-1}; nmr (CCl_4) δ 3.62 (s, 3 H), 3.15 (t, 2 H), 2.2 (t, 2 H), 2.0–1.0 (m, 19 H).

Methyl 6-iodohexanoate, prepared in 87% yield from 6-bromohexanoic acid using obvious modifications of the procedure described above, had bp 75–78° (0.2 Torr) [lit.[20] bp 83–87° (0.8 Torr)]; ir (CCl_4) 1741 cm^{-1}; nmr (CCl_4) δ 3.60 (s, 3 H), 3.18 (t, 2 H), 2.27 (t, 2 H), 2.0–1.2 (m, 6 H).

6-Benzoxy-1-chlorohexane. 1-Chloro-6-hydroxyhexane (100 g, 0.73 mol) was dissolved in 400 ml of THF in a three-necked, 1-l. round-bottomed flask equipped with a magnetic stirring bar. Benzyl chloride (126.6 g, 1.0 mol) was added to the flask. Sodium hydride (20 g, 0.83 mol) was added in portions to this reaction mixture. Hydrogen was evolved during the sodium hydride addition. After the sodium hydride had been added, the reaction mixture was refluxed for 12 hr. At this point, TLC (CH_2Cl_2, silica gel) showed the reaction to be complete, and the reaction mixture was cooled to room temperature and quenched by cautiously pouring it into 1 l. of saturated aqueous ammonium chloride solution. The organic layer was separated and combined with two 200-ml ether washes of the aqueous layer. The organic layer was washed with 100 ml of saturated sodium chloride, dried ($MgSO_4$), and concentrated to an oil with a rotary evaporator. Distillation of this oil yielded 100.6 g (61%) of 1-benzoxy-6-chlorohexane: bp 110–112° (0.15 Torr) [lit.[21] bp 136–141° (1 Torr)]; ir (neat) 3085, 3062, 3030, 1100 cm^{-1}; NMR (neat) δ 7.15 (m, 5 H), 4.33 (s, 2 H), 3.3 (m, 4 H), 1.0–1.9 (m, 8 H).

2,2-Dimethylbutyne was prepared in 32% yield according to the procedure of Collier and Macomber.[22]

Ethyl 21-Docosenoate. 11-Undecenylmagnesium chloride was prepared from 11-chloroundecene and magnesium turnings in THF using standard procedures (*ca.* 97% yield). Cuprous iodide (19 g, 100 mmol), purified as described previously,[23] was placed in a flame-dried, 1-l. round-bottomed flask equipped with a magnetic stirring bar. Addition of 200 ml of THF gave a suspension which was cooled to −78°. A 2.2 *M* ether solution of methyllithium (45 ml, 99 mmol) was added to this suspension with a syringe. The reaction mixture was stirred for 1 hr at −78°. The resulting light yellow suspension was allowed to warm gradually to 0° with stirring. The resulting suspension of methylcopper was cooled to −78° and 71 ml of a 1.4 *M* THF solution of 11-undecenylmagnesium chloride (99 mmol) was added with a syringe. The reaction mixture was allowed to stir at −78° for another hour and warmed until a solution formed. The resulting purple solution was immediately cooled to −78°, during which time some white solid formed. Ethyl 11-iodoundecanoate (41 g, 120 mmol) was added with a syringe. The resulting suspension was stirred with an overhead stirrer for 1 hr at −78°, after which time it was allowed to come to room temperature. The reaction mixture was stirred for 2 hr at room temperature before it was quenched by pouring into a saturated aqueous ammonium chloride solution. The ethereal solution was separated and the aqueous phase was extracted with three 250-ml portions of ether. The combined organic fractions were washed once with 200 ml of saturated sodium chloride and dried (Na_2SO_4). The product, ethyl 21-docosenoate (28.5 g, 79%), was isolated by removing the ether with a rotary evaporator and recrystallizing the resulting oil from ethanol. The product was greater than 99% pure by GLC and had ir (CCl_4) 1734 and 1639 cm^{-1}; NMR ($CDCl_3$) δ 5.4–6.3 (m, 1 H), 4.8–5.2 (m, 2 H), 4.15 (q, 2 H), 1.0–2.6 (m, 41 H); mass spectrum (70 eV) parent peak *m/e* 366. For characterization, this material was hydrolyzed to 21-docosenoic acid (20% refluxing aqueous sodium hydroxide solution, 24 hr). After recrystallization from methanol, the acid had mp 69–70° (lit.[24] mp 62–63°); ir (CCl_4) 1710 cm^{-1}; NMR ($CDCl_3$) δ 8.6 (br, 1 H), 5.5–6.2 (m, 1 H), 4.8–5.2 (m, 2 H), 1.0–2.5 (m, 38 H); mass spectrum (70 eV) parent peak *m/e* 338.

Anal. Calcd for $C_{22}H_{42}O_2$: C, 78.04; H, 12.50. Found: C, 77.82; H, 12.28.

Ethyl 17-Benzoxyheptadecanoate. Using the procedure described for ethyl 21-docosenoate, 6-benzoxyhexylmagnesium chloride was prepared from 6-benzoxy-1-chlorohexane and allowed to react with methylcopper and ethyl 11-iodoundecanoate to give ethyl 17-benzoxyheptadecanoate in 64% yield on a 200-mmol scale. The product ester was recrystallized from ethanol and had mp 34.5–35°; ir (CCl_4) 1740, 1180, 1103, 720, and 693 cm^{-1}; NMR (CCl_4) δ 7.2 (s, 5 H), 4.4 (s, 2 H), 4.03 (m, 2 H), 3.37 (t, 2 H), 2.2 (t, 2 H), 1.1–1.9 (broad s, 31 H).

Anal. Calcd for $C_{26}H_{44}O_3$: C, 77.18; H, 10.96. Found: C, 76.91; H, 10.89.

Ethyl Heptacosanoate. A copper(I) ate complex was prepared from 50 mmol of methylcopper(I) and 68 ml of 0.75 *M* hexadecylmagnesium bromide in THF using the procedures described above for 10-undecenylmagnesium chloride. In this case, an overhead stirrer was used to facilitate stirring of the reaction mixture. This ate complex was alkylated with ethyl 11-iodoundecanoate and worked up as described above by hydrolysis with saturated aqueous ammonium chloride and extraction with three 300-ml portions of benzene. After recrystallization from ethanol, the product ethyl heptacosanoate (18.5 g, 87% yield) had mp 61.5–62° (lit.[25] mp 62.5–62.6°), ir (CCl_4) 1740 cm^{-1}.

Diethyl tetratriacontanedioate was prepared on a 25-mmol scale from 1,12-dodecyldi(magnesium bromide) and ethyl 11-iodoundecanoate according to the procedures described above. The product diester (12.7 g, 85% yield) was isolated by recrystallization from ethanol and had mp 76–77.5°, nmr (CCl_4) δ 4.07 (m), 2.25 (t), 1.8–1.0 (m), 1.25 (br s).

Anal. Calcd for $C_{38}H_{74}O_4$: C, 76.71; H, 12.54. Found: C, 77.07; H, 12.27.

Dimethyl tetracosanedioate was prepared from 1,12-didodecylmagnesium bromide and methyl 6-iodohexanoate on a 50-mmol scale according to the procedures described above. The product diester was isolated in 72% yield by recrystallization from methanol and had mp 69–71° (lit.[26] mp 69–70°), ir (CCl_4) 1741 cm^{-1}.

Methyl 12-Methylheptadecanoate. A 100-mmol aliquot of 2-heptylmagnesium bromide was allowed to react with methylcopper(I) (100 mmol) in the manner described above to give a copper(I) ate complex. During this procedure, care was taken to avoid allowing the ate complex to decompose by cooling the solution of the ate complex to −78° as soon as a distinct purple color appeared in the reaction mixture (ca. 10°). Alkylation with methyl 11-iodoundecanoate (110 mmol) and subsequent work-up yielded an oil which was distilled. The product, methyl 12-methylheptadecanoate, had bp 135–140° (0.2 Torr) and was isolated in 54% yield (16.1 g). A small forerun contained an additional amount of product according to TLC (~3 g), but this forerun was not redistilled. Methyl 12-methylheptadecanoate thus obtained had ir (CCl_4) 1740 cm^{-1} and mass spectrum (70 eV) parent peak *m/e* 298.

Anal. Calcd for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83. Found: C, 76.11; H, 12.60.

Use of 2,2-Dimethylbutynylcopper(I) in Selective Copper(I) Ate Complex Alkylations. A red-orange ether solution of 2,2-dimethylbutynylcopper was prepared from 2,2-dimethylbutynyllithium and copper(I) iodide according to the procedure of House and Umen.[27] Cooling this solution of copper(I) acetylide to −78° gave a yellow solution. This color change was reversible. Ad-

dition of 0.7 ml of a 1.5 *M* THF solution of 10-undecenylmagnesium chloride (1 mmol) to 1 mmol of this copper acetylide at −78° gave a red-orange solution of a copper ate complex. Warming this solution to room temperature resulted in no color changes other than some slight darkening. In alkylation reactions, the alkyl halide was added by syringe at −78 to this copper ate complex. After stirring at −78° for 0.5 hr, these solutions were allowed to gradually warm to room temperature. The reactions were hydrolyzed with 0.1 ml of hydrochloric acid after 2–3 hr of stirring at room temperature and analyzed by GLC on an 8-ft, SE-30 column.

Registry No.—11-Chloroundecene, 872-17-3; 10-undecenol, 112-43-6; carbon tetrachloride, 56-23-5; ethyl 11-iodoundecanoate, 53821-20-8; 11-bromoundecanoic acid, 2834-05-1; methyl 11-iodoundecanoate, 929-33-9; methyl 6-iodohexanoate, 14273-91-7; 6-bromohexanoic acid, 4224-70-8; 6-benzoxy-1-chlorohexane, 53821-21-9; 1-chloro-6-hydroxyhexane, 2009-83-8; benzyl chloride, 100-44-7; ethyl 21-docosenoate, 53821-22-0; 21-docosenoic acid, 53821-23-1; ethyl 17-benzoxyheptadecanoate, 53821-24-2; ethyl heptacosanoate, 53821-25-3; methylcopper(I), 1184-53-8; diethyl tetratriacontanedioate, 53821-26-4; dimethyl tetracosanedioate, 26134-71-4; methyl 12-methylheptadecanoate, 2490-24-6; 2,2-dimethylbutynylcopper(I), 53821-27-5.

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The Mechanism of the Reaction of Alkyl Bromides and Iodides with Mercury(II) and Silver(I) Fluorides[1]

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Received November 1, 1974

The conversion of representative alkyl bromides and iodides to alkyl fluorides by mercury(II) and silver(I) fluoride has been shown to involve generation of intermediate alkyl carbonium ions by comparison of the product distributions obtained on conversion with those observed on solvolysis of related alkyl derivatives. Treatment of *exo*-2-bromo-*endo*-2-chloronorbornane (1) and *endo*-2-bromo-*exo*-2-chloronorbornane (2) with either mercury(II) or silver(I) fluoride yields *endo*-2-chloro-*exo*-2-fluoronorbornane (8) as the only fluorine-containing epimer. The extensive elimination observed in the reaction of *cis*- and *trans*-4-*tert*-butylcyclohexyl bromide (3 and 4) with both mercury(II) and silver(I) fluoride, as well as the substantial fraction of *cis*- and *trans*-3-*tert*-butylcyclohexyl fluorides produced, parallels the related product ratios observed from the solvolysis of *cis*- and *trans*-4-*tert*-butylcyclohexyl arenesulfonates. Treatment of 1-iodo-2-phenylethane-2,2-d_2 (5) with mercury(II) or silver(I) fluoride produces a 1:1 mixture of 1-fluoro-2-phenylethane-2,2-d_2 and 1-fluoro-2-phenylethane-1,1-d_2. Similar treatment of 1-iodo- or 1-bromooctane produces a mixture of 1- and 2-fluorooctane while conversion of 2-iodo- or 2-bromooctane yields 2-fluorooctane, exclusively. The C–F bond-forming step in these reactions is suggested as proceeding by the intermolecular transfer of fluoride from a halometallo–ate complex to a carbonium ion center.

The biological activity[2] of organic compounds containing isolated fluorine atoms and the utility of the ^{19}F nucleus as a probe of molecular structure[3] are in large part responsible for the continuing interest in monofluoro-substituted organic compounds. The introduction of a single fluorine atom into an organic molecule is, therefore, a reaction of some importance and a variety of reagents are useful for this purpose.[4,5] For complex molecules, however, the direct replacement of an isolated halogen atom, particularly bromine or iodine, by reaction with mercury(II) or silver(I) fluoride has frequently proven the procedure of choice for such syntheses, since these reactions proceed under mild conditions.[5]

The major fraction of evidence pertinent to the mechanism of the reaction of halocarbons with mercury(II) or silver(I) fluoride is stereochemical in nature. Conversion of 16β-bromo-17α,20:20,21-bis(methylenedioxy)-Δ^4-pregnen-3-one into 16β-fluoro-17α,20:20,21-bis(methylenedioxy)-Δ^4-pregnen-3-one and of α-1-bromo-2,3,4,6-tetraacetyl-D-galactose into β-1-fluoro-2,3,4,6-tetraacetyl-D-galactose by silver(I) fluoride are reported to proceed, respectively, with predominant retention[6] and inversion[7] of configuration. A concerted reaction[8] might be expected to lead to products with retained or inverted stereochemistry while a nonconcerted process might be expected to yield, in general, products with loss of stereochemistry. Without complementary

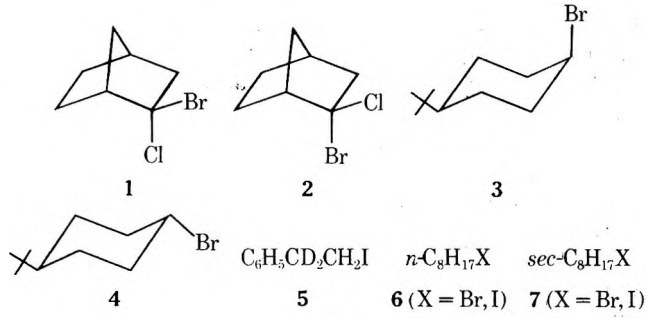
Table I
Reaction of *exo*-2-Bromo-*endo*-2-chloronorbornane (1) and *endo*-2-Bromo-*exo*-2-chloronorbornane (2) with Silver(I) and Mercury(II) Fluoride at 0° in Pentane

MF_x	Substrate	Product rel yield,[a,b] % 8[d]	9[e]
AgF[f]	1[g]	>97	c
HgF_2[h]	1	>97	c
AgF	2[i]	>97	c
HgF_2	2	>97	c

[a] As determined by ^{19}F nmr;[10] estimated accuracy ± 3%. [b] Absolute yields ranged between 10 and 20%. [c] None observed. Under the conditions of analysis a relative yield of <3% would not have been detected. [d] Registry no., 49633-61-6. [e] Registry no., 49633-64-9. [f] Registry no., 7775-41-9. [g] Registry no., 21690-94-8. [h] Registry no., 7783-39-3. [i] Registry no., 21690-95-9.

examination of the stereochemical course of the reaction of the second diastereomer, no convincing stereochemical or mechanistic generalizations can be drawn from these studies.

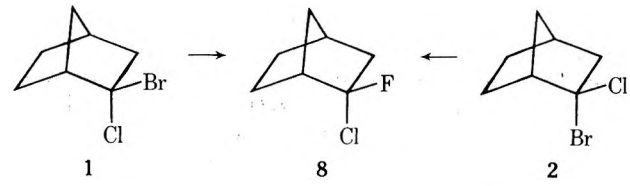
Our interest in this class of reactions has prompted us to resolve the stereochemical and mechanistic ambiguities posed by previous studies by examination of the reactions of mercury(II) and silver(I) fluoride with *exo*-2-bromo-*endo*-2-chloronorbornane (1) and *endo*-2-bromo-*exo*-2-chloronorbornane (2), *cis*- and *trans*-4-*tert*-butylcyclohexyl bromide (3 and 4), 1-iodo-2-phenylethane-*2,2-d*$_2$ (5), and 1- and 2-iodo- and -bromooctane (6 and 7). Here we wish to report that the product distributions observed on conversion of these halides are consistent with a nonconcerted mechanism involving intermediate carbonium ions.



Results

Reaction of *exo*-2-Bromo-*endo*-2-chloronorbornane (1), *endo*-2-Bromo-*exo*-2-chloronorbornane (2), and *cis*- and *trans*-4-*tert*-Butylcyclohexyl Bromide (3 and 4). As a first step in establishing the mechanism of the reaction of mercury(II) and silver(I) fluoride with alkyl halides, we have examined the reaction of *exo*-2-bromo-*endo*-2-chloronorbornane (1) and *endo*-2-bromo-*exo*-2-chloronorbornane (2) with these reagents (Table I). Studies of the solvolysis of norbornyl derivatives have established the nearly exclusive preference of the norbornyl cation for exo product formation.[9] Thus, the production of *endo*-2-chloro-*exo*-2-fluoronorbornane (8) as the only fluorine-containing epimer from reaction of both 1 and 2 would suggest the possibility that these reactions involve intermediate carbonium ions.

Treatment of 1 or 2 with mercury(II) or silver(I) fluoride in pentane at 0° yielded, within the limits of detection, *exo*-2-fluoro-*endo*-2-chloronorbornane, exclusively. To make certain that these results do not simply reflect loss of stereochemistry in the starting halide, these reactions were carried to ~50% completion. Comparison of the ir spectra

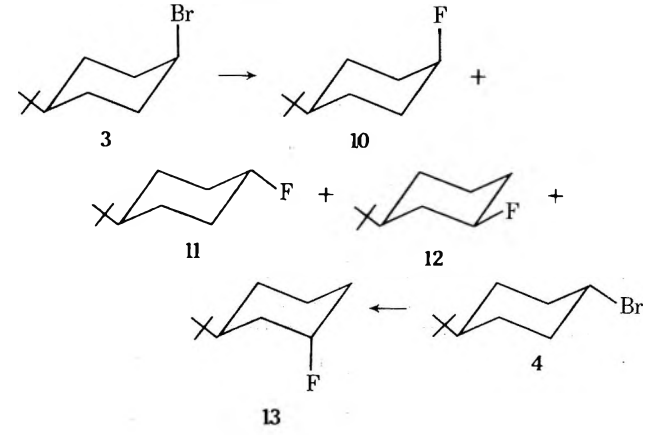


of the recovered starting material established that in these reactions no loss of stereochemistry in the starting material accompanies reaction. The stereochemical integrity of the potential product *exo*-2-chloro-*endo*-2-fluoronorborane[10] (9) under reaction conditions was similarly established.

The conversion of both 1 and 2 to 8 implicates a carbonium ion intermediate in these reactions. However, in view of the recognized nature of 2-substituted norbornyl derivatives to participate in carbonium ion processes when such processes are not always observed in more general systems, a parallel stereochemical study was carried out.

Solvolysis studies performed on *cis*- and *trans*-4-*tert*-butylcyclohexyl derivatives do not reveal a preferred product stereochemistry but are characterized by significant loss of stereochemistry at the 1 carbon, giving rise to epimeric product mixtures. Moreover, appreciable yields of *cis*- and *trans*-3-*tert*-butylcyclohexyl derivatives occur, presumably as the result of Wagner–Meerwein rearrangement. Significantly, the predominant products in all instances are olefins, produced by competing elimination reactions.[11]

The relative yields of fluorine-containing products from the reaction of 3 and 4 with silver(I) fluoride are summarized in Table II. Product ratios were determined by ^{19}F NMR using the characteristic assignments identified by Eliel and Martin.[12] A similar product distribution was observed in the reaction of 3 and 4 with mercury(II) fluoride. The principal product in all instances was *tert*-butylcyclohexene. These results, summarized in Table II, are clearly consistent with the reaction of 3 and 4 with mercury(II) and silver(I) fluoride as involving an intermediate carbonium ion. The origin of the considerable differences between the relative yields of products 10 and 11 and 12 and 13 produced from 3 and 4 is not entirely evident, but may reflect ion-pairing effects.



Reaction of 1-Iodo-2-phenylethane-*2,2-d*$_2$ (5), 1- and 2-Iodooctane and 1- and 2-Bromooctane (6 and 7). Solvolysis studies of β-phenethyl derivatives have shown that 1,2-aryl migration proceeds concomitantly with ionization.[13] Thus, the presence of rearranged product from the reaction of 5 with mercury(II) and silver(I) fluoride can only imply the intermediacy of a carbonium ion pathway in these reactions.

1-Iodo-2-phenylethane-*2,2-d*$_2$ (5) was obtained by treating 2-phenylethanol-*2,2-d*$_2$ (14) with *N*-methyl-*N,N'*-dicyclohexylcarbondiimidium iodide.[14] Reduction of 5 with tri-

Table II
Relative Yields of *tert*-Butylcyclohexyl Fluorides from the Reaction of *cis*- and *trans*-4-*tert*-Butylcyclohexyl Bromide (3 and 4) with Silver(I) and Mercury(II) Fluoride in Pentane

			Product rel yield, %[a]			
MF_x	Substrate	Temp, °C	10[c]	11[d]	12[e]	13[f]
AgF	3[g]	−20[b]	6	13	19	62
AgF	4[h]	−20[b]	40	35	13	12
HgF_2	3	0	15	6	5	74
HgF_2	4	0	60	7	13	20

[a] Analysis performed by ^{19}F NMR. The extensive decomposition of compounds 10–13 under analysis conditions prevented their determination by GLC. Product balances of fluorine-containing products as determined by ^{19}F NMR ranged between 10 and 20%. *tert*-Butylcyclohexenes comprised the predominant products in these reactions. [b] Reactions carried out at 25 and 0° yielded no detectable fluorine-containing products. [c] Registry no., 20259-37-4. [d] Registry no., 20259-36-3. [e] Registry no., 20272-31-5. [f] Registry no., 20272-35-9. [g] Registry no., 5009-36-9. [h] Registry no., 5009-37-0.

Table III
Yield and Composition of 1-Fluoro-2-phenylethane-d_2 Obtained on Reaction of 1-Iodo-2-phenylethane-2,2-d_2 with Silver(I) and Mercury(II) Fluoride in Pentane

			Product rel yield, %[a]		
MF_x	Temp, °C	Reaction time, hr	$PhCD_2CH_2F$[c]	$PhCH_2CD_2F$[d]	Product abs yield,[b] %
AgF	36	1			94
	25	2			70
	0	3	50	50	87
	−20	5			88
HgF_2	36	3			73
	25	7	50	50	25
	0	20			30
	−20	60			30

[a] Determined by ^1H NMR. [b] Analysis performed by GLC on 10 ft × 0.25 in. column of SE-30 on Chromosrob G. [c] Registry no., 50561-93-8. [d] Registry no., 53907-37-2.

n-butyltin hydride yielded exclusively and quantitatively phenylethane-2,2-d_2, thereby confirming the position of isotopic substitution.

$$C_6H_5CH_2CO_2CH_3 \xrightarrow[CH_3OD]{CH_3ONa} C_6H_5CD_2CO_2CH_3 \xrightarrow{LiAlH_4} C_6H_5CD_2CH_2OH$$

14

$$14 + [C_6H_{11}N{=}C{=}N(CH_3)C_6H_{11}]I \longrightarrow C_6H_5CD_2CH_2I$$

5

$$5 \xrightarrow{(n\text{-}C_4H_9)_3SnH} C_6H_5CD_2CH_3$$

Examination of the ^1H NMR spectrum of the 1-fluoro-2-phenylethane-d_2 isolated from the reaction of **5** with mercury(II) and silver(I) fluoride revealed equal amounts of 1-fluoro-2-phenylethane-1,1-d_2 and -2,2-d_2 (Table III).

$$C_6H_5CD_2CH_2I \xrightarrow[M = Ag(I),\ Hg(II)]{MF_x} C_6H_5CD_2CH_2F + C_6H_5CH_2CD_2F$$

Control experiments established that the starting halide **5** did not isomerize in the presence of mercury(II) fluoride under reaction conditions. Similar experiments indicated that **5** is partially isomerized (~20%) by silver(I) fluoride under corresponding reaction conditions.

To determine if, in fact, product isomerism was occurring during the course of the reaction, authentic 2-phenyl-1-fluoroethane-2,2-d_2 was prepared as outlined below and

$$C_6H_5CD_2CH_2OTs \xrightarrow[110°,\ 15\ Torr]{KF\text{-}DEG} C_6H_5CD_2CH_2F$$

subjected to the influence of reaction conditions. The recovered material showed no evidence, as determined by ^1H NMR, of having undergone rearrangement.

In complementary experiments, 1-iodo- and 1-bromooctane were both treated with mercury(II) and silver(I) fluoride. The results, summarized in Table IV, show that, inter alia, a substantial quantity of 2-fluorooctane is produced in these reactions. To exclude the possibility that this product arises via readdition of hydrogen fluoride to 1-octene, the products produced by β-elimination of hydrogen fluoride from initially formed 1-fluorooctane, these reactions were repeated in the presence of 1-decene. The failure to observe any 2-fluorodecane in the reaction products demonstrates that readdition of eliminated hydrogen fluoride is not taking place in these and by inference in similar reactions described above. Furthermore, the formation of 2-fluorooctane suggests that a Wagner–Meerwein rearrangement is occurring. Taken together, these results further implicate a carbonium ion pathway in these reactions.

Several additional features of the data of Table IV are noteworthy. First, it is apparent that reaction temperature significantly affects product distribution and overall yields in the reaction of 1-iodo-, but not 2-iodooctane, with both mercury(II) and silver(I) fluoride. Lower reaction temperatures clearly favor a higher yield of 1-fluorooctane from silver(I) fluoride while the same reaction with mercury(II) fluoride appears to proceed in higher yields at higher temperatures. Second, comparison of these results and those in Tables I–III suggests that silver(I) fluoride is superior overall to mercury(II) fluoride for the preparation of simple monofluorinated organic compounds from the corresponding alkyl iodide or bromide.

Finally, a comparison of the different product ratios resulting from the reaction of 1- and 2-bromo- and 1- and 2-iodooctane with mercury(II) and silver(I) fluoride and those recently reported by Liotta and Harris[4] for the reaction of 1- and 2-bromooctane with potassium fluoride in the presence of 18-crown-6 ether merits brief attention. These limited data suggest that the 18-crown-6 ether complex of potassium fluoride may be superior to mercury(II) and silver(I) fluoride for the conversion of a primary alkyl halides to the corresponding alkyl fluoride but that mercury(II) and silver(I) fluorides provide higher yields of secondary alkyl fluorides from the corresponding alkyl bromides and iodides. Moreover, in our hands, potassium fluoride reacted with 1-iodo-2-phenylethane in benzene solution in the presence of 18-crown-6 ether to yield styrene exclusively, while treatment of the same substrate with either mercury(II) or silver(I) fluoride results in high yields of 1-fluoro-2-phenylethane. These facts suggest that, while the KF–18-crown-6 ether reagent may be useful for certain conversions, further studies of this system need to be carried out before any definitive statement regarding the scope of this reagent can be made.

Discussion

The fact that the production of alkyl fluorides by reaction of alkyl iodides and bromides with mercury(II) and silver(I) fluorides involves a heterogeneous reaction makes a detailed investigation of this reaction difficult. This diffi-

Table IV
Products from the Reaction of Silver(I) and Mercury(II) Fluorides with 1-Iodo-, 1-Bromo-, 2-Iodo-, and 2-Bromooctane

MF_x	Alkyl halide	Registry no.	Reaction time, hr	Temp, °C	Solvent	Product,[a] % *n*-Alkyl fluoride	Product,[a] % *sec*-Alkyl fluoride	Product,[a] % Olefin[b]
AgF	$1\text{-}C_8H_{17}I$	629-27-6	2	36	Pentane	38	33	25
			4	25	Pentane	48	24	22
			10	0	Pentane	49	26	21
			24	−20	Pentane	59	14	14
HgF_2	$1\text{-}C_8H_{17}I$		5	36	Pentane	41	14	4
			6	25	Pentane	31	11	1
			24	0	Pentane	25	17	2
			48	−20	Pentane	14	16	1
AgF	$2\text{-}C_8H_{17}I$	557-36-8	1	25	Pentane	<1	56	34
			2	0	Pentane	<1	65	32
			3	−20	Pentane	<1	63	28
			10	−78	Pentane	<1	56	39
HgF_2	$2\text{-}C_8H_{17}I$		1	25	Pentane	<1	48	28
			2	0	Pentane	<1	57	31
			4	−20	Pentane	<1	65	26
			10	−78	Pentane	<1	57	11
AgF	$1\text{-}C_8H_{17}Br$	111-83-1	24	36	Pentane	9	59	14
			48	25	Pentane	8	46	13
HgF_2	$1\text{-}C_8H_{17}Br$		24	36	Pentane	23	27	2
			48	25	Pentane	10	25	3
AgF	$2\text{-}C_8H_{17}Br$	557-35-7	5	36	Pentane	<1	65	16
			6	25	Pentane	<1	55	20
			24	0	Pentane	<1	58	23
			48	−20	Pentane	<1	61	23
HgF_2	$2\text{-}C_8H_{17}Br$		1	36	Pentane	<1	54	18
			2	25	Pentane	<1	61	22
			5	0	Pentane	<1	68	18
			24	−20	Pentane	<1	58	8
KF[e]–18-crown-6	$1\text{-}C_8H_{17}Br$		128[c,d]	90	Benzene	92[c]	<1[c]	8[c]
KF–18-crown-6	$2\text{-}C_8H_{17}Br$		240[c,d]	90	Benzene	<1[c]	32[c]	68[c]
KF–18-crown-6	$C_6H_5CH_2CH_2I$	17376-04-4	96[d]	90	Benzene	<1	<1	99

[a] As determined by GLC on a 20 ft × 0.25 in. column of SE-30 on Chromosorb G. [b] No effort was made to distinguish between 1- and 2-octene, which had identical retention times under the conditions of analysis. [c] Taken from ref 4. [d] Time for one-half conversion of starting materials to products. [e] Registry no., 7789-23-3.

culty is compounded by the sometime instability of the alkyl fluoride product. Nonetheless, the stereochemical and product studies presented above establish that the production of alkyl fluorides in these reactions proceeds through intermediate carbonium ions. The detailed nature of the C–F bond-forming step in these reactions has not been delineated, although it could conceivably proceed by the intermolecular transfer of fluoride from a halometallo–ate complex to a carbonium ion center.

In conclusion, it should be recalled that the influence which heteroatom-containing neighboring groups play in determining product stereochemistry in solvolysis reactions is well known and provides a satisfactory explanation for the apparent conflict in stereochemical conclusions reached in earlier work,[6,7] since both results are consistent with the involvement of a carbonium ion intermediate accompanied by neighboring group participation.[15]

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were determined within sodium chloride cells on a Perkin-Elmer Model 225 grating spectrophotometer. NMR (^1H and ^{19}F) spectra were determined with a Varian T-60 NMR spectrometer at 60 and 56.4 MHz, respectively. ^1H chemical shifts are reported in parts per million relative to internal tetramethylsilane. All coupling constants are in hertz. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-7E mass spectrometer. Samples for spectral and elemental analyses were purified on a Hewlett-Packard Model 700 thermal conductivity gas chromatograph. Analytical GLC analyses were performed on a Hewlett-Packard Model 5750 flame ionization instrument. Absolute yields of products were calculated from peak areas using internal standard techniques with response factors obtained from authentic samples.

Several commercial sources of mercury(II) and silver(I) fluoride were used in this study. No obvious differences in results were observed when reasonable caution was taken to exclude moisture during storage and handling. Pentane was deolefinated and deoxygenated prior to use.

***exo*-2-Bromo-*endo*-2-chloronorbornane (1) and *exo*-2-chloro-*endo*-2-bromonorbornane (2),** bp 41–42 (1.0 Torr) and 83–85°(9.0 Torr), respectively [lit.[16] bp 42–49° (0.06 Torr)], were prepared by treating 2-chloronorborn-2-ene and 2-bromonorborn-2-ene with anhydrous hydrogen bromide and hydrogen chloride, respectively, as described by Fry.[16]

***endo*-2-Chloro-*exo*-2-fluoronorbornane (8) and *exo*-2-Chloro-*endo*-2-fluoronorbornane (9).** Authentic samples of these substances were prepared by literature procedures.[10]

***cis*- and *trans*-4-*tert*-butylcyclohexyl bromide (3 and 4)** were prepared according to the procedures described by Eliel and

Martin.[12b] Tri-*n*-butyltin hydride was prepared by a modification[17] of the literature procedure.[18]

Methyl-1-phenyl-2,2-d_2 Acetate. Under a flush of nitrogen, sodium (150 mg, 6.5 mg-atoms) was placed into a flame-dried, three-necked, 250-ml flask equipped with a reflux condenser. All remaining arms were stoppered with serum caps and methanol-*O*-*d* (100 g, 99% *d*) and methyl phenylacetate (7.5 g, 50 mmol) were added by syringe. This mixture was refluxed for 12 hr under a static head of nitrogen, then neutralized by addition of aqueous deuterium chloride (240 mg of a 30% solution of deuterium chloride in deuterium oxide). The resulting mixture was concentrated at reduced pressure to yield 6.5 g (87%) of crude methyl-1-phenyl-2,2-d_2 acetate: ^{1}H NMR (CCl_4) δ 7.20 (5 H, s), 3.58 (3 H, s).

2-Phenylethanol-2,2-d_2. Into a three-necked, 250-ml flask equipped with a Teflon-coated magnetic stirrer bar, an addition funnel, and a condenser and containing a solution of 0.91 g (24 mmol) of lithium aluminum hydride in 100 ml of anhydrous ether was added a solution of crude methyl-1-phenyl-2,2-d_2 acetate (6.0 g, 40 mmol) in 40 ml of anhydrous ether. The rate of addition was such that a gentle reflux was maintained. This mixture was subsequently refluxed for 2 hr, cooled, and poured into 70 ml of cold, 15% sulfuric acid. The ether layer was separated and the aqueous phase extracted with three 50-ml portions of ether. The combined organic layers were extracted with a solution (50 ml) of saturated aqueous sodium bicarbonate followed by a final extraction with 50 ml of water, then dried ($MgSO_4$) and concentrated under reduced pressure to yield 4.5 g (91%) of crude 2-phenylethanol-2,2-d_2: ^{1}H NMR (CCl_4) δ 7.20 (5 H, s), 3.65 (2 H, s), 3.10 (1 H, s).

***N*-Methyl-*N,N'*-dicyclohexylcarbodiimidium iodide** was synthesized as described by Scheffold and Saladin,[14] mp 109.5–111.5° (lit.[14] mp 111–113°).

1-Iodo-2-phenylethane-2,2-d_2 (5). Crude 2-phenylethanol-2,2-d_2 (4.5 g, 36 mmol) was added to a stirred solution of 25.1 g (72.0 mmol) of freshly prepared *N*-methyl-*N,N'*-dicyclohexylcarbodiimidium iodide in 400 ml of anhydrous THF contained in a 500-ml flask. The resulting solution was stirred at 35° for 3 hr and the volatile components were subsequently removed under reduced pressure. The remaining brown oil was taken up in 400 ml of hexane which was then extracted with three 200-ml portions of methanol–water (4:1). The combined aqueous washings were extracted with three 150-ml portions of hexane. All hexane layers were combined, dried over Na_2SO_4, and percolated through 80 g of silica gel (40–140 mesh), before concentrating at reduced pressure. Distillation of the residual oil yielded 6.7 g (78% based on crude 2-phenylethanol-2,2-d_2, 57% overall from methyl phenylacetate) of 1-iodo-2-phenylethane-2,2-d_2: bp 65–68° (0.5 Torr) [lit.[19] (undeuterated) bp 95° (3 Torr)]; ^{1}H NMR (CCl_4) δ 7.21 (5 H, s), 3.27 (2 H, s); 96% d_2 as indicated by mass spectral analysis.

Reduction of 1-Iodo-2-phenylethane-2,2-d_2 (5) with Tri-*n*-butyltin Hydride. Into a flame-dried, 40-ml centrifuge tube was placed 0.50 g (2.1 mmol) of 1-iodo-2-phenylethane-2,2-d_2 and 10 mg of AIBN. The vessel was capped with a rubber septum and flushed with nitrogen before adding 2 ml of pentane and 0.87 g (3.0 mmol) of tri-*n*-butyltin hydride by syringe. The mixture was photolyzed at 25° for 1 hr with a hand scanner. Excess tri-*n*-butyltin hydride was destroyed by the addition of 0.46 g of carbon tetrachloride and the resulting phenylethane-1,1-d_2 analyzed by glpc on a 6-ft, 10% SE-30 column. Analysis of the ^{1}H NMR of a collected sample indicated >97% phenylethane-1,1-d_2.

Preparation of 2-Phenylethyl *p*-Toluenesulfonate-2,2-d_2. *p*-Toluenesulfonyl chloride (4.80 g, 25.2 mmol) was added to an ice-cooled, stirred solution of 2.50 g (20.0 mmol) of freshly distilled 2-phenylethanol-2,2-d_2 in 7.0 ml of pyridine over a 15-min period. The resulting mixture was stirred for an additional 15 min at 0° and then for 6 hr at room temperature before pouring it into 100 ml of water. The mixture was then extracted with four 100-ml portions of ether. The combined ether layers were washed with two 100-ml portions of water, dried ($CaSO_4$), and concentrated. The oily residue was recrystallized from pentane, yielding 2.58 g, mp 38–39°; second crop (0.14 g), mp 38.5–39.5° [lit.[20] (undeuterated) mp 39–40°] (total yield 50%); ^{1}H NMR (CCl_4) δ 7.8–7.0 (9 H, m) 4.11 (2 H, s), 2.37 (3 H, s).

Preparation of 2-Phenyl-1-fluoroethane[21] and 2-Phenyl-1-fluoroethane-2,2-d_2. Into a 25-ml, two-necked flask containing a Teflon-coated stirrer bar was placed 1.00 g (3.62 mmol) of 2-phenylethyl-*p*-toluenesulfonate-2,2-d_2 and 1.05 g (18.1 mmol) of anhydrous potassium fluoride. One neck was capped with a rubber septum and the other connected to a flame-dried cold trap. The apparatus was flushed with nitrogen as the trap was cooled to −78°. Anhydrous diethylene glycol (5.0 ml) was added by syringe and the mixture allowed to stir for 3 hr at 110° (15 Torr). The trap was allowed to warm to room temperature under a nitrogen atmosphere and found to contain 0.37 g of a liquid which GLC analysis indicated to be 4% styrene and 96% 2-phenyl-1-fluoroethane-2,2-d_2 (81% overall yield): ^{1}H NMR (2-phenyl-1-fluoroethane-2,2-d_2) (CCl_4) δ 7.17 (5 H, s), 4.46 [2 H, d, J(HCF) = 47 Hz]; 95% d_2 as indicated by mass spectral analysis.

General Procedures. Similar procedures were used in carrying out the reaction of all alkyl halides with mercury(II) and silver(I) fluorides. Representative examples are given below.

Reaction of *endo*-2-Bromo-*exo*-2-chlorononorbornane (2) with Mercury(II) Fluoride. Into a flame-dried, nitrogen-flushed, 25-ml flask equipped with a condenser and a Teflon-coated stirrer bar was placed 0.14 g (0.59 mmol) of mercury(II) fluoride. A solution of 0.10 g (0.48 mmol) of *endo*-2-bromo-*exo*-2-chlorononorbornane in dry pentane (10 ml) was added by syringe. The mixture was stirred for 12 hr at 25° at which time GLC analysis of an aliquot indicated the complete consumption of **2**. The resulting mixture was filtered through diatomaceous earth and the product, *endo*-2-chloro-*exo*-2-fluoronorbornane, was collected by preparative GLC using a 40 ft × 0.25 in. column of 7% Zonyl E-7 on Chromosorb W. Its ir spectrum and GLC retention time were identical with those of authentic *endo*-2-chloro-*exo*-2-fluoronorbornane (8).[10]

Reaction of *exo*-2-Bromo-*endo*-2-chlorononorbornane (1) with Silver(I) Fluoride. Under a flush of nitrogen, silver(I) fluoride (0.14 g, 1.1 mmol) was placed into a flame-dried 25-ml flask equipped with a Teflon-coated stirrer bar and condenser. A solution of 0.10 g (0.49 mmol) of *exo*-2-bromo-*endo*-2-chlorononorbornane in 10 ml of dry pentane was added by syringe. The resulting mixture was stirred until GLC analysis indicated the complete disappearance of starting halide (12 hr at 25°). The resulting mixture was gravity filtered and subjected to preparative GLC on a 40 ft × 0.25 in. column of Zonyl E-7. The collected product, *endo*-2-chloro-*exo*-2-fluoronorbornane (8), had ir and GLC retention time identical with those of an authentic sample.[10]

Reaction of *cis*-4-*tert*-Butylcyclohexyl Bromide (3) with Silver(I) Fluoride. Into a chilled (−20°), flame-dried flask equipped with a condenser and a Teflon-coated stirrer bar and containing 1.5 g (12 mmol) of silver(I) fluoride, was injected by syringe a cold (−20°) solution of 1.0 g (4.6 mmol) of *cis*-4-*tert*-butylcyclohexyl bromide in 10 ml of dry pentane. The mixture was stirred at −20° for 12 hr, gravity filtered, and concentrated under reduced pressure. GLC analysis could not be carried out because of extensive product decomposition under analysis conditions. Product ratios were determined by ^{19}F NMR using the chemical shift values for *cis*- and *trans*-4- and -3-*tert*-butylcyclohexyl fluoride reported by Eliel and Martin.[12a]

Reaction of 1-Iodo-2-phenylethane-2,2-d_2 (5) with Silver(I) Fluoride. Anhydrous silver(I) fluoride (1.4 g, 11 mmol) was placed in a 50-ml flame-dried flask containing a Teflon-coated stirrer bar. The flask was capped with a rubber septum, flushed with nitrogen, and cooled to 0° before adding by syringe a cold (0°) solution of 1.2 g (5.1 mmol) of 1-iodo-2-phenylethane-2,2-d_2 in 10 ml of dry pentane. The resulting mixture was stirred under a static head of nitrogen for 3 hr and gravity filtered and the clear solution was distilled, bp 65–66° (35 Torr) [lit.[21] bp 55–56° (12 Torr)], to yield 0.31 g of a 1:1 mixture of 1-fluoro-2-phenylethane-1,1-d_2 and -2,2-d_2: ^{1}H NMR (CCl_4) δ 7.14 (5 H, s), 4.50 [2 H, d, J(HCF) = 47 Hz], 2.94 [2 H, d, J(H–C–CF) = 21 Hz).

Reaction of 1-Iodooctane with Silver(I) Fluoride. Into a 25-ml flame-dried flask equipped with a condenser and a Teflon-coated stirrer bar was placed 1.2 g (9.5 mmol) of silver(I) fluoride. The condenser was capped with a rubber septum and a solution of 1.00 g (4.20 mmol) of 1-iodooctane and 0.504 g of *n*-decane (GLC standard) in 10 ml of dry pentane was added by syringe. The resulting mixture was stirred at 25° for 4 hr, at which time GLC analysis indicated that consumption of the starting halide was complete. The reaction mixture was gravity filtered and the product distribution determined by GLC analysis on a 20 ft × 0.25 in. column of 7.5% SE-30 on Chromosorb G. The principal components in order of increasing elution time were octene(s), 2-fluorooctane, and 1-fluorooctane. The GLC retention time, ^{1}H NMR, ir, and mass spectra of collected samples of 1-fluorooctane were identical with those of an authentic sample of 1-fluorooctane.[22] The spectral properties of a collected sample of the second component were consistent with its assignment as 2-fluorooctane: ir (CCl_4) 870 cm^{-1} (vs, C–F); ^{1}H NMR (CCl_4) δ 4.50 [1 H, d of multiplets, J(H–C–F) = 48 Hz], ~1.4 [10 H, br, complex multiplet, $(CH_2)_5$], 1.26 [3 H, d of d, J(CH_3–CHF) = 23 Hz, J(CH_3–CHF) = 7.0 Hz], 0.96 (3 H, t).

No attempt was made to separate the possible isomers of octene.

Reaction of *sec*-Octyl Iodide with Mercury(II) Fluoride. Mercury(II) fluoride (1.2 g, 5.0 mmol) was placed in a 25-ml, flame-dried flask equipped with a condenser and a Teflon-coated stirrer bar. The condenser was capped with a rubber septum and the flask cooled to −20° under a flush of nitrogen. A cold (−20°) solution of 1.00 g (4.16 mmol) of *sec*-octyl iodide and 0.502 g of decane (GLC internal standard) in 10 ml of dry pentane was injected by syringe. The disappearance of *sec*-octyl iodide was followed by glpc. After 5 hr at −20° consumption of starting halide was complete. The resulting mixture was filtered through diatomaceous earth and the clear solution analyzed by GLC using a 20 ft × 0.25 in. column of 7.5% SE-30 on Chromosorb G.

Reaction of 1-Bromooctane with Silver(I) Fluoride. Into a flame-dried, 25-ml flask equipped with a condenser and a Teflon-coated stirrer bar was placed 1.4 g (11 mmol) of silver(I) fluoride. The condenser was capped with a rubber septum and the vessel flushed with nitrogen before injecting by syringe a solution of 1-bromooctane (1.0 g, 5.16 mmol) and 0.512 g of *n*-decane (GLC internal standard) in 10 ml of pentane. This mixture was stirred at 25° until GLC analysis indicated the complete disappearance of starting halide (~48 hr). The solution was gravity filtered and product distribution determined by GLC analysis on a 20 ft × 0.25 in. column of 7.5% SE-30 on Chromosorb G.

Reaction of 2-Bromooctane with Mercury(II) Fluoride. Mercury(II) fluoride (1.5 g, 6.3 mmol) was placed in a 25-ml, flame-dried flask equipped with a condenser and a Teflon-coated stirrer bar. The condenser was capped with a rubber septum and the vessel flushed with nitrogen before injecting by syringe a solution of 2-bromooctane (1.01 g, 5.20 mmol) and 0.492 g of *n*-decane (GLC internal standard) in 10 ml of dry pentane. The resulting mixture was stirred at room temperature until the disappearance of starting halide was complete as indicated by GLC (~2 hr). The suspended solids were removed by filtration through diatomaceous earth and the solution components analyzed by GLC on a 20 ft × 0.25 in. column of 7.5% SE-30 on Chromosorb G.

Reaction of 1-Iodo-2-phenylethane with Potassium Fluoride in the Presence of 18-Crown-6 Ether. Into a two-necked, 25-ml flask equipped with a Teflon-coated stirrer bar was placed 1.0 mmol of 18-crown-6 ether[23] and 0.58 g (10 mmol) of anhydrous potassium fluoride[24] which had been previously dried at 110° for 12 hr. One neck was stoppered with a rubber septum and to the other neck was attached a small distilling head. Anhydrous benzene (11 ml) was added by syringe and reaction vessel heated under a static head of nitrogen until 1 ml of distillant had been collected. The distillation head was replaced with a flame-dried condenser and 1-iodo-2-phenylethane (1.16 g, 5.00 mmol) added by syringe. The resulting mixture was heated with vigorous stirring at 90°. The extent of reaction was monitored periodically by GLC analysis. After 96 hr, ~50% of the starting halide had been consumed. GLC analysis indicated the presence of <1% 1-fluoro-2-phenylethane. The resulting mixture was gravity filtered and concentrated by distillation. Distillation of the residue afforded 0.20 g of styrene, identical by GLC retention time, ir, and nmr with a commercial sample.

Recovery of *cis*-4-*tert*-Butylcyclohexyl Bromide (3) from Partial Conversion Using Mercury(II) and Silver(I) Fluoride. Into a flame-dried, nitrogen-flushed, 40-ml centrifuge tube equipped with a Teflon-coated stirrer bar was placed 0.063 g (0.50 mmol) of silver(I) fluoride. The tube was capped with a rubber septum, flushed with nitrogen, and cooled to −20° before adding by syringe a cold (−20°) solution of 0.22 g (1.0 mmol) of **3** in 2 ml of dry pentane. The mixture was stirred at −20° for 12 hr and gravity filtered, and the solution components were separated and analyzed by GLC using a 40 ft × 0.25 in. column of Zonyl E-7 on Chromosorb G.

The equivalent procedure was carried out using mercury(II) fluoride. In both instances, GLC analysis of the unreacted starting bromide indicated that no (<1%) isomerism had occurred.

Recovery of 1-Iodo-2-phenylethane-*2,2-d*$_2$ (5) from Partial Conversion Using Mercury(II) and Silver(I) Fluoride. A chilled (0°) solution of **5** (1.00 g, 4.30 mmol) in 10 ml of dry pentane was added by syringe to a 25-ml flask equipped with a Teflon-coated stirrer bar and a serum-capped condenser and containing 0.50 g (2.1 mmol) of mercury(II) fluoride. This mixture was stirred for 4.5 hr at 0°, then gravity filtered and concentrated in vacuo. Distillation of the residual liquid afforded ~0.1 g of 1-fluoro-2-phenylethane-*1,1*- and -*2,2-d*$_2$, bp 58–61° (25 Torr), and 0.51 g of 1-iodo-2-phenylethane-*d*$_2$, bp 95° (3.0 Torr), the ^{1}H NMR spectrum of which revealed that no (<3%) isomerism to 1-iodo-2-phenylethane-*1,1-d*$_2$ had occurred. Repetition of this experiment using silver(I) fluoride revealed that ~20% of the recovered starting halide had isomerized to 1-iodo-2-phenylethane-*1,1-d*$_2$.

Reaction of 1-Iodooctane with Mercury(I) and Silver(I) Fluoride in the Presence of 1-Decene. Silver(I) fluoride (1.4 g, 11 mmol) was placed in a flame-dried, 25-ml flask equipped with a Teflon-coated stirrer bar and a condenser capped with a rubber septum. The vessel was flushed with nitrogen before adding by syringe a solution of 1-iodooctane (1.20 g, 5.00 mmol) and 1-decene (0.50 ml) in 10 ml of dry pentane. The resulting solution was stirred for 4 hr at 25° and gravity filtered and the solution components were determined by GLC analysis on a 20 ft × 0.25 in. column of 7.5% SE-30 on Chromosorb G. The equivalent reaction was repeated using mercury(II) fluoride. In both instances no (<1%) 2-fluorodecane was observed.

Recovery of 2-Phenyl-1-fluoroethane-*2,2-d*$_2$ from Treatment with Mercury(II) and Silver(I) Fluoride. 2-Phenyl-1-fluoroethane (0.10 g, 0.80 mmol) was placed in a flame-dried 25-ml flask equipped with a Teflon-coated stirrer bar and containing 0.24 g (1.0 mmol) of mercury(II) fluoride suspended in 2.0 ml of pentane under an atmosphere of nitrogen. After 24 hr, the mixture was gravity filtered. Examination of the recovered starting material by ^{1}H NMR showed no evidence of any rearrangement. Likewise, the material recovered from a similar reaction using silver(I) fluoride was unchanged from that of authentic 2-phenyl-1-fluoroethane-*2,2-d*$_2$.

Acknowledgment. The experimental assistance of Mr. George M. Anderson in the initial course of this investigation is gratefully acknowledged.

Registry No.—**5**, 53907-38-3; 14, 51086-45-4; methyl phenyl-2,2-*d*$_2$-acetate, 50848-70-9; 2-phenylethyl-2,2-*d*$_2$ *p*-toluenesulfonate, 53907-39-4.

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Reduction as a Side Reaction Arising from the Thermal Decomposition of Lithium Organocuprates to Form Copper Hydride Derivatives[1]

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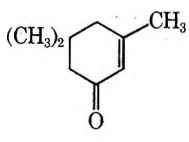
Received August 28, 1974

Earlier studies of the thermal decomposition of alkylcopper(I) derivatives[2] have indicated that, when possible, alkylcopper compounds **1** decompose by elimination of a copper hydride derivative **2** that may reduce an additional molar equivalent of the alkylcopper compound **1** to form copper(0). The copper(0) may catalyze further decomposition of the original organocopper compound.[2c] Except for derivatives [e.g., $(CH_3Cu)_n$] that cannot readily eliminate CuH, most organocopper compounds (including the lithium organocuprates) begin to undergo thermal decomposition somewhere within the temperature range −30 to 0°. This thermal decomposition problem [accompanied by formation of black colloidal Cu(0)] is aggravated by the fact that reaction of copper(I) salts with RLi reagents to form $(RCu)_n$ or $(R_2CuLi)_n$ reagents often fails to occur when the *temperature of the reaction mixture* is below the range −50 to −30°. Also, the cuprate reagents, $(R_2CuLi)_n$, often react only very slowly with other substrates at *reaction solution temperatures* below −20 to −30°. Thus, the reaction temperatures required to form and use $(R_2CuLi)_n$ reagents are often approximately the same as the temperatures where thermal decomposition becomes a serious competing reaction.[3]

$$\underset{\mathbf{1}}{(R{-}CH_2CH_2{-}Cu{-}ligand)_n} \longrightarrow RCH{=}CH_2 + H{-}Cu{-}ligand \quad (\mathbf{2})$$

We wish to call attention to the fact that when the reaction conditions selected permit competing thermal decomposition leading to a CuH derivative, a side reaction leading to reduction may also be observed. Such a competing reduction was observed during the conjugate addition of the mixed cuprate reagent, *t*-BuC≡CCu(Li)CH=CH_2, to isophorone (**3**).[3] In order to obtain a reasonable reaction rate for the conjugate addition, the reaction was run in a temperature range (−20 to 0°) where competing thermal decomposition of the cuprate reagent was occurring. The formation of the saturated ketone **4** as a by-product sug-



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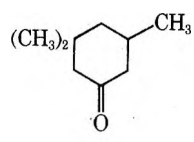

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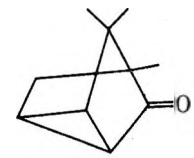
gested that a copper hydride derivative had been formed by elimination from a vinylcopper species. In the reaction of several epoxides with (*n*-Bu)$_2$CuLi at 0–25°, by-products resulting from reduction of the epoxides were observed.[4] The authors surmised that these by-products were derived from CuH derivatives and found that this side reaction could be practically eliminated by performing the reactions in the presence of excess *n*-BuLi. In another instance where the saturated ketone **5** was stirred with (*n*-Bu)$_2$CuLi at 0° (a temperature where thermal decomposition is usually observed) for 1 hr, the authors observed that the only product formed was the alcohol **6**.[5] These observations again suggest the occurrence of a reduction arising from a CuH derivative formed by thermal decomposition.



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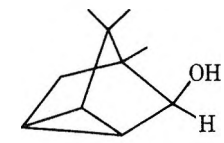

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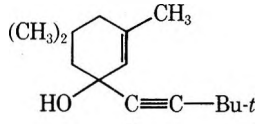
Several recent studies indicate that certain CuH derivatives may serve as reducing agents. Although polymeric $(CuH)_n$, prepared as an Et_2O-insoluble solid,[2a] is itself thermally unstable, decomposing to Cu(0) and H_2 at temperatures above −20°, the material does reduce various alkyl and aryl halides as well as organocopper compounds.[2a] A thermally stable, insoluble complex metal hydride having the stoichiometry $LiCuH_2$, prepared from Me_2CuLi in $LiAlH_4$,[6] may also be useful as a reducing agent. A reagent, presumed to be a CuH derivative, prepared by the reaction of CuI with $LiAlH(OMe)_3$ at 0° has been found to reduce various halides, sulfonates, and epoxides.[7] Also, solutions prepared by reaction of the insoluble $(CuH)_n$[2a] with 1 molar equiv of one of the RLi derivatives, LiOBu-*t*, LiSPh, LiC≡CPr-*n*, LiC≡CBu-*t*, or LiBu-*n*, in Et_2O, THF, or THF–HMP solution at −20 to −40°, have been found to reduce various halides, sulfonate esters, and the C=C of unsaturated carbonyl compounds.[8] These latter reagents were suggested[8] to have the stoichiometry LiCuHR.

To examine the question of what types of CuH derivatives were likely to reduce unsaturated carbonyl compounds, we treated the enone **3** with a cold, ethereal *suspension* of $(CuH)_n$,[2a] with a cold ethereal *solution* of the *n*-Bu_3P complex[2a] of CuH, and with a PhH *solution* of the thermally more stable crystalline hexameric complex, $[Ph_3PCuH]_6$.[9] In no case did we observe formation of the dihydro ketone **4**. Since the formation and separation of $(CuH)_n$ by the previously described[2a] reduction of CuBr with *i*-Bu_2AlH in pyridine is tedious, we tried unsuccessfully to form comparable, well-defined material by reaction of the soluble complex, (*n*-$Bu_2S)_2CuI$, with *i*-Bu_2AlH in cold heptane, Et_2O–heptane, or Et_2O–PhH. Although the solution, formed at −35°, decomposed (depositing either black colloidal Cu or a Cu mirror on the wall of the reaction vessel) when warmed suggesting the presence of some CuH derivative, we were unable to separate any well-defined product.

Preformed solid $(CuH)_n$ did not dissolve when treated with an Et_2O solution of *t*-BuC≡CLi. However, when the solvent was changed to THF, the $(CuH)_n$ dissolved upon treatment with ~0.3 molar equiv of *t*-BuC≡CLi at −40° to form a brown solution. Because the original $(CuH)_n$ product contains a substantial amount (~25%)[2a] of pyridine that complicated measuring its weight, we treated the solid $(CuH)_n$ with just sufficient amounts of a cold (−40°) THF solution of *t*-BuC≡CLi to obtain a solution and then ana-

lyzed aliquots of the solution for Cu and Li. The ratio Cu/Li determined for these solutions was 2.6, consistent with the formation of a reagent having a stoichiometry three CuH to one *t*-BuC≡CLi. This cold (−27°) THF solution reduced the enone **3** to the ketone **4** and the yield of **4** (46–48%) was approximately the same with or without added HMP (cf. ref 8a). If excess *t*-BuC≡CLi was used so that solutions of stoichiometry 1:1 CuH to *t*-BuC≡CLi were prepared, the yield of reduction product was lowered and higher boiling by-products were produced. Materials with comparable spectra and GLC behavior were formed by treatment of the enone **3** with *t*-BuC≡CLi, suggesting that these higher boiling by-products were formed from the 1,2 adduct **7**. This observation is compatible with our other ob-



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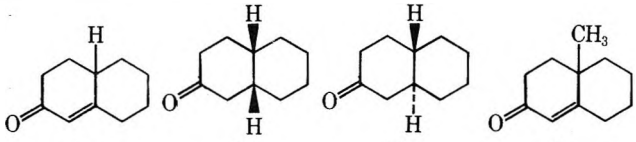
servations indicating that the reducing agent formed from CuH and *t*-BuC≡CLi does not have a 1:1 stoichiometry, as would be the case for the formulation LiCuHR. Consequently, our data are consistent with the suggestion that the side reaction leading to reduction during a conjugate addition reaction can be attributed to partial decomposition of the cuprate reagent to form a CuH derivative, provided an organolithium reagent is present in the mixture. However, the CuH derivative formed in the presence of *t*-BuC≡CLi does not correspond to the previously described reagents, LiCuH(C≡CPr-*n*)[8] and LiCuHBu-*n*,[8b] either in its stoichiometry or in its response to added HMP.[8a]

We also examined the reduction of the enone **8** with a cold (−27°) THF solution of the reagent *t*-BuC≡CLi-$(CuH)_3$. As with isophorone (**3**), reduction occurred slowly to form a mixture of saturated ketones **9** (87% of the mixture) and **10** (13% of the mixture). This same trend, favoring formation of the cis isomer, was also observed in reduction of the enone **11** with either *n*-PrC≡CCuHLi[8a] or *n*-BuCuHLi.[8b]



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

To explore the seeming discrepancy in stoichiometry further we treated an excess of preformed[2a] $(CuH)_n$ with a THF solution of *n*-BuC≡CLi and analyzed the resulting solution for Cu content. Interestingly, with this *n*-alkylacetylide the stoichiometry was 1:1 *n*-BuC≡CLi to CuH, corresponding to the stoichiometry reported[8] when $(CuH)_n$ was treated with *n*-PrC≡CLi. Thus, for reasons we regard as obscure the THF solution formed from $(CuH)_n$ and *n*-BuC≡CLi has the stoichiometry LiCuH(C≡CBu-*n*) whereas the analogous solution formed from *t*-BuC≡CLi has the stoichiometry *t*-BuC≡CLi$(CuH)_3$.

Experimental Section[10]

Preparation of Reagents and Reactants. The preparations or sources and standardization procedures used for *t*-BuC≡CH,[3] *n*-BuC≡CH,[11b] ketones **4**, **9**, and **10**,[11a] and halide-free ethereal MeLi,[3] CuI,[3] CuBr,[3] and $(n\text{-Bu})_2SCuI$[3] are described in earlier publications. Reaction of *t*-BuC≡CH with 1.0 equiv of MeLi at 0° in either Et_2O or THF was used to form solutions of *t*-BuC≡CLi. An analogous procedure was used to obtain a THF solution of *n*-BuC≡CLi. Commercial samples of *i*-Bu_2AlH were transferred in a drybox to give a 0.835 *M* solution in PhH or a 0.764 *M* solution in heptane. Previous directions[9] were followed to obtain $(Ph_3P \cdot CuH)_6$ as red crystals, mp 105–107° (sealed capillary) (lit.[9] mp 111°). In a typical preparation of $(CuH)_n$,[2a] a cold (−40°) solution of 0.72 g (5.0 mmol) of CuBr in 50 ml of pyridine was treated with 7.2 ml of a heptane solution containing 5.5 mmol of *i*-Bu_2AlH_2. After the mixture, which became red-brown in color, had been stirred at −40° for 10 min, it was diluted with Et_2O while keeping the temperature in the range −30 to −78°, and the resulting brown $(CuH)_n$ precipitate was separated by centrifugation. The solid was washed with three portions of cold (−40 to −78°) Et_2O before use. When the solid was treated with a cold (−40 to −78°) solution of 4 ml of *n*-Bu_3P in 15 ml of Et_2O, practically all the solid dissolved to give a brown solution. This solution was treated with 0.70 g (5.1 mmol) of the enone **3** in 5 ml of Et_2O and the resulting solution was allowed to warm from −40 to 25° over several hours. The crude neutral product, recovered in the usual way, was distilled in a short-path still to separate 0.39 g (56%) of the starting enone **3** (GLC analysis, silicone SE-30 on Chromosorb P, retention time 9.8 min) that contained none of the saturated ketone **4** (6.9 min).

To examine the stoichiometry of solutions prepared from $(CuH)_n$, samples of $(CuH)_n$ were prepared[2a] at −30 to −40° from 1.44 g (10 mmol) of CuBr, 70 ml of pyridine, and a solution of 11 mmol of *i*-Bu_2AlH in 11.4 ml of heptane. Addition of excess cold Et_2O precipitated the $(CuH)_n$, which was washed in a centrifuge tube with three portions of cold (−40 to −78°) Et_2O before use. A portion of the $(CuH)_n$ was treated with a cold (−27°) solution of 4.02 mmol of *t*-BuC≡CLi in 14 ml of THF and the cold mixture was shaken and then centrifuged. Aliquots of the cold supernatant solution were withdrawn, and quenched in H_2O. Each aliquot was analyzed for Li content by flame photometry and for Cu content by electrodeposition. The mole ratio of Cu/Li was 2.6 (average of three determinations). In a similar experiment a $(CuH)_n$ sample was treated with a cold solution of 4.99 mmol of *n*-BuC≡CLi in 25 ml of THF. After mixing and centrifugation, an aliquot of the supernatant solution was removed, quenched, and analyzed. The Cu/Li mole ratio was 1.2.

Reduction of Enone 3 with the CuH–*t*-BuC≡CLi Reagent. A solution of this reagent was obtained by treatment of the $(CuH)_n$, from 1.44 g (10.0 mmol) of CuBr and 11.0 mmol of *i*-Bu_2AlH, with a solution of *t*-BuC≡CLi, from 0.32 g (3.9 mmol) of *t*-BuC≡CH, 3.85 mmol of MeLi, and 18 ml of THF, while the temperature of the reaction mixture was maintained at −40 to −78°. The solution of the CuH derivative was treated with 232 mg (1.68 mmol) of the enone **3** in 3 ml of THF, then stirred at −27° for 10 hr, and finally allowed to warm to 0°. The resulting solution was washed with aqueous NH_4Cl, filtered through Celite, mixed with a known weight of *n*-$C_{12}H_{26}$ (an internal standard), and analyzed employing a GLC apparatus (silicone SE-30 on Chromosorb P) calibrated with known mixtures of authentic samples. The components present were *n*-$C_{12}H_{26}$ (retention time 15.4 min), ketone **4** (8.2 min, 48% yield), and enone **3** (11.6 min, 22% recovery). Collected (GLC) samples of ketones **3** and **4** were identified with authentic samples by comparison of GLC retention times and ir and mass spectra. In several cases the collected ketone **4** was contaminated with a few percent of the β,γ-unsaturated isomer of enone **3**.

When the same reaction was repeated except that 2 ml of HMP was added just before the addition of the enone **3**, there were obtained a 46% yield of ketone **4** and a 45% recovery of enone **3**. A comparable reaction was performed in which the $(CuH)_n$, from 10 mmol of CuBr, was treated with 10 mmol of *t*-BuC≡CLi before the addition of 1.68 mmol of the enone. In this case the GLC curve of the crude product exhibited peaks corresponding to *n*-$C_{12}H_{26}$ (15.2 min), ketone **4** (8.6 min), enone **3** (12.4 min), and three additional higher boiling components (22.6, 24.4, and 26.8 min).

To obtain evidence concerning the nature of these higher boiling by-products, a cold (−27°) solution of *t*-BuC≡CLi, from 0.74 g (9.0 mmol) of *t*-BuC≡CH and 9.0 mmol of MeLi in 18 ml of THF, was treated with 0.41 g (3.0 mmol) of the enone **3** in 3 ml of THF. The reaction solution was stirred overnight while it was allowed to warm to 25° and then it was partitioned between Et_2O and aqueous NH_4Cl and the Et_2O solution was dried and concentrated. The crude neutral product, 0.63 g of yellow liquid, had ir absorption (CCl_4) at 3600, 3450 (free and associated OH), 2240 (C≡C), and 1668 cm^{-1} (weak, conjugated C=O) indicating the presence of the adduct **7** accompanied by some unchanged enone **3**. The GLC curve of this crude product exhibited peaks corresponding to the unchanged enone **3** (11.9 min) and three partially resolved components with retention times (22.6, 24.5, and 26.8 min) corresponding to the three previously described by-products. A collected (GLC) sample of a mixture of these three components exhibited ir absorption at 2220 (conjugated C≡C), 1640, and 1610 cm^{-1} (C=C) and

the mass spectrum of the mixture exhibited the following abundant peaks: *m/e* (rel intensity) 202 (82), 187 (100), 145 (34), 131 (23), 57 (81), and 41 (21). These spectroscopic properties are consistent with the formulation of these by-products (mol wt 202) as various double-bond isomers formed by dehydration of the alcohol **7** during the GLC analysis and separation.

Reduction of the Octalone 8 with the CuH–*t*-BuC≡CLi Reagent. The CuH, from 1.44 g (10.0 mmol) of CuBr and 11 mmol of *i*-Bu_2AlH in 12.4 ml of heptane, was dissolved in a cold (−40 to −78°) solution of 3.85 mmol of *t*-BuC≡CLi in 18 ml of THF and the resulting cold (−27°) solution was treated with a solution of 254 mg (1.69 mmol) of the octalone **8** in 3 ml of THF. The resulting solution was stirred at −27° for 10 hr and then allowed to warm to 0° and subjected to the previously described isolation procedure. The crude neutral product was mixed with 28.0 mg of *n*-$C_{14}H_{30}$ (an internal standard) and subjected to analysis (GLC, Apiezon L on Chromosorb P) employing equipment that had been calibrated with known mixtures of authentic samples. The reaction product contained *n*-$C_{14}H_{30}$ (retention time 11.5 min), the trans ketone **10** (16.9 min, yield 5%), the cis ketone **9** (19.0 min, yield 34%), and the starting ketone **8** (33.0 min, recovery 46%). Collected (GLC) samples of each of the ketone products **9** and **10** were identified with an authentic sample by comparison of ir and mass spectra and GLC retention times.

Registry No.—**3**, 78-59-1; **7**, 53783-16-7; **8**, 1196-55-0; $(CuH)_n$, 53783-17-8; *t*-BuC≡CLi, 37892-71-0; *t*-BuC≡CLi$(CuH)_3$, 53849-09-5.

References and Notes

(1) This research has been supported by Public Health Service Grant No. RO1-GM-20197 from the National Institute of General Medical Sciences. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer.

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(10) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 NMR spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

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Stereoselectivity in the Base-Catalyzed Decarboxylation of 4-*tert*-Butylcyclohexane-1,1-dioic Acid[1]

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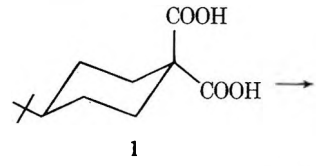
Received August 22, 1974

We recently reported the results of an investigation of the stereoselectivity of base-catalyzed decarboxylation of 5,5-dicarboxy-2-isopropyl-1,3-dioxane.[2] The product composition was found to be quite sensitive to the basic solvent chosen for the reaction. We were puzzled, however, by the apparent lack of sensitivity of the product composition in decarboxylation of 4-phenylcyclohexane-1,1-dioic acid to the solvent; 2,4,6-trimethylpyridine and 1,3,5-trimethylbenzene gave essentially the same result.[3] This prompted us to synthesize 4-*tert*-butylcyclohexane-1,1-dioic acid (**1**), study the diastereomeric composition of the product using a number of basic solvents, and compare these results to those of the 1,3-dioxane system.

Table I
Product Composition in the Decarboxylation of 4-*tert*-Butylcyclohexane-1,1-dioic Acid

Solvent	% 2 at 100.0°[a]
Pyridine	70.7 ± 0.5
2-Methylpyridine	70.3 ± 0.5
2,6-Dimethylpyridine	77.3 ± 0.6
N,*N*-Dimethylaniline	72.4 ± 0.6
N,*N*-Dimethylformamide	69.1 ± 1.3

[a] All errors are standard deviations.



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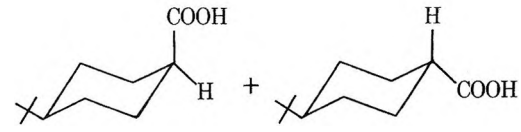
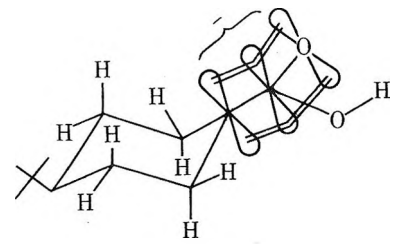


2 **3**

A modified Birch reduction[4] of 4-*tert*-butylbenzoic acid produced 4-*tert*-butyl-1,5-cyclohexadien-1-oic acid (**4**). Two moles of hydrogen was consumed per mole of **4** using a palladium on carbon catalyst, and a mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanoic acid was produced. Treatment of this mixture with diazomethane, carboxylation,[5] and hydrolysis gave **1**.

The results of base-catalyzed decarboxylation of **1** are given in Table I. The product composition is independent of the per cent yield. The investigation is limited by the fact that **1** was sparingly soluble in aniline and *N*-methylaniline. The diastereomeric product composition is indeed dependent on the choice of basic solvent. If the reasonable assumption is made that the step which controls the stereochemical outcome of decarboxylation of 5,5-dicarboxy-2-isopropyl-1,3-dioxane, *i.e.*, protonation of the enediol intermediate, also obtains in the present study, our results may



be readily explained by comparing the steric hindrance encountered in approach of the conjugate acid of the basic solvent to the upper and lower faces of the intermediate. The syn-axial hydrogens render attack from above more difficult than attack at the lower face. As the bulk of the groups surrounding the acidic site increases, the selectivity increases. The identical product composition (within ex-

perimental error) for pyridine and 2-methylpyridine is possibly due to the fact that the 2-methylpyridinium ion can orient itself in such a manner that the methyl group is positioned away from the syn-axial hydrogens of the ring; such an orientation is not possible for 2,6-dimethylpyridine.

It is of interest that our stereochemical results are comparable to those found in reactions involving approach of a reagent to an exocyclic double bond of a cyclohexane system. Zimmerman and Mariano[6] found that protonation of the enol of 4-phenyl-1-acetylcyclohexane using 2,4,6-trimethylpyridine hydrochloride produced 62 and 78% of the cis isomer in methanol and acetonitrile, respectively. Hydroboration–oxidation[7] and catalytic hydrogenation[8] of 1-methylene-*tert*-butylcyclohexane both produce a preponderance of cis isomer. In each case, the approach is from the less hindered lower face of the molecule.

The lower faces of the cyclohexane and 1,3-dioxane rings are virtually identical.[9] The ratios of the rate of axial attack on the enediol intermediate in the 1,3-dioxane system to that in the cyclohexane system may be readily calculated to be 3.43, 4.22, 2.64, and 18.6 for pyridine, 2-methylpyridine, 2,6-dimethylpyridine, and *N,N*-dimethylaniline, respectively. It is not surprising that the more congested environment of the sp^3 hydridized nitrogen of the *N,N*-dimethylanilinium ion is more selective than the sp^2 hybridized nitrogens in the pyridinium ions.

The anomalously low rate ratio in 2,6-dimethylpyridine shows that an effect in opposition to the steric effect is at work. An attractive possibility is that the transition state in tautomerization of the 1,3-dioxane system is stabilized by coordination of the conjugate acid of the basic solvent to the syn-axial nonbonded electron pairs of the ring oxygens. Since acidity of pyridinium ions decreases as methyl substitution increases, stabilization by coordination becomes less important as the solvent is changed from pyridine to 2-methylpyridine to 2,6-dimethylpyridine.

The fact that 69.7% of **2** is produced in DMF is somewhat surprising. Protonation of the intermediate is undoubtedly by a proton itself, since DMF is too weakly basic for its conjugate acid to be formed in significant concentration. Zimmerman[10] has found that the thermodynamically more stable isomer is the major product when the size of the proton donor decreases. One would expect a larger proportion of the more stable **3** with the tiny proton in DMF, than with the much larger conjugate acids of the basic solvents. One possible explanation is that the effective size of a solvated proton in DMF is quite large. We are currently investigating the effect of the polarity of the solvent on the diastereomeric product composition.

Experimental Section

Gas chromatographic analyses were obtained using a Hewlett-Packard Research Chromatograph, Model 7620A. The nmr spectra were recorded on an Hitachi Perkin-Elmer R-24 nmr spectrometer. Microanalyses were performed by the Baron Consulting Company, Orange, Conn.

4-*tert*-Butylcyclohexane-1,1-dioic Acid. To a dry 2-l. round-bottom three-necked flask, equipped with a mechanical stirrer, a Dry Ice–acetone condenser, and a 100 ml graduated, pressure equalizing addition funnel equipped with a gas inlet adapter was added 51.2 g (287 mmol) of 4-*tert*-butylbenzoic acid and 325 ml of anhydrous diethyl ether. The resulting suspension was stirred while the condenser was filled with Dry Ice–acetone, and the flask was externally cooled with a Dry Ice–acetone bath. Anhydrous ammonia was then admitted to the flask until *ca.* 900 ml of liquid had condensed. The solution was vigorously stirred and 8.6 g of lithium, cut into small pieces each weighing *ca.* 0.3 g, was added over a period of 30 min. After 5 min of stirring, 75 ml of absolute ethanol was cautiously added to the blue solution. When the blue color had disappeared, stirring was stopped, the condenser and cooling bath were removed, and the ammonia and ether were allowed to evaporate. The orange residue was acidified with 1 l. of 6 *M* HCl as the mixture was cooled with an ice–water bath. The precipitate was removed by filtration and dried in a desiccator, yielding 36.9 g (71.0%) of product: pmr (CCl_4) δ 0.90 (s, 9 H), 2.3 (d, J = 3 Hz, 2 H), 5.81 (d, J = 10 Hz, 1 H), 6.38 (d, J = 10 Hz, 1 H), 7.02 (m, 1 H), 11.80 (s, 1 H). The product was tentatively identified as 4-*tert*-butyl-1,5-cyclohexadien-1-oic acid by the method of synthesis[11] and comparison of its pmr spectrum with that of 4-isopropyl-1,5-cyclohexadien-1-oic acid.[4]

A solution of 30.0 g (167 mmol) of product dissolved in 350 ml of diethyl ether was hydrogenated in a Parr apparatus using 0.25 g of 5% palladium on carbon with an initial hydrogen pressure of 60 psi. After the theoretical amount of hydrogen had been taken up, the reaction mixture was filtered through a Celite pad, and concentrated on the rotary evaporator, producing 28.9 g (94.0%) of a white solid, which was shown by treatment with diazomethane and glpc analysis (*vide infra*) to be a mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanoic acid containing a small amount of unreacted 4-*tert*-butylbenzoic acid.

To a 500 ml erlenmeyer flask containing a Teflon coated magnetic stirring bar was added 8 g of KOH dissolved in 15 ml of H_2O. A solution of 40 ml of methanol and 15 ml of diethyl ether was added, and the mixture was chilled to 0°. A solution of 30.0 g (140 mmol) of Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) in 350 ml of diethyl ether is added in small portions, behind a lab shield. After the addition was complete, the mixture was stirred for an additional 10 min, and then cooled to −60°. The solution was decanted and added in small portions to 25.0 g (139 mmol) of the mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanoic acid dissolved in 300 ml of diethyl ether, until the yellow color due to CH_2N_2 persisted. Excess CH_2N_2 was destroyed by the dropwise addition of glacial acetic acid. Most of the solvent was removed on the rotary evaporator, and final concentration was carried out at 50° and 0.5 Torr, producing 26.3 g (95.0%) of an orange oil.

A mixture of the diastereomeric 1-carbomethoxy-4-*tert*-butylcyclohexanoic acids was prepared in 60% yield from the orange oil following the procedure of Reffers, Wynberg, and Strating.[5] Addition of 5.0 g (21 mmol) of the oil to 50 ml of 20% ethanolic KOH produced a mass of white crystals in 10 min. Filtration gave 4.3 g of the crude dipotassium salt, which was dissolved in 20 ml of H_2O, chilled in an ice–water bath, and acidified with 20 ml of 6 *M* HCl. The resulting mixture was saturated with NaCl and filtered to yield 4.1 g (86%) of diacid. Two recrystallizations from benzene gave fine white needles, mp 165–166°.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.21; H, 8.93.

Decarboxylation Studies. A solution of 50.0 mg of 4-*tert*-butylcyclohexane-1,1-dioic acid, *n*-butyl benzoate (30.0 to 40.0 mg, the internal standard), and 5.00 ml of freshly distilled base was prepared in a dry weighing bottle. Samples of 1.5 ml of this solution were transferred to each of three 5-ml ampoules which had been dried overnight in an oven at 120°. The ampoule was then connected to a vacuum system, plunged into a bath of liquid N_2, evacuated to 0.1 Torr, and sealed. After warming to room temperature, the ampoules were immersed in a silicone oil bath maintained at 100.0° for a period of 24 hr. The ampoules were then plunged into liquid N_2, warmed to room temperature, and opened. Each decarboxylation product was mixed with 5 g of crushed ice in a test tube, and 5 ml of concentrated HCl was added dropwise with swirling. A test with litmus paper established the acidity of the mixture. Extraction with five 2-ml portions of diethyl ether was performed by means of a Pasteur pipet. The combined ether extracts were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was treated with diazomethane as described previously.[2] The mixture of esters was analyzed by glpc (3 ft × 0.25 in., 15% Carbowax 20M on Chromosorb W, 80–100 mesh at 155°, He flow 98 ml/min). The results reported in Table I for each solvent represent the average values of at least 15 glpc analyses. A correction factor for the extraction and analysis was determined using a synthetic mixture of pure *cis*- and *trans*-4-*tert*-butylcyclohexanoic acid. Control experiments demonstrated that epimerization did not occur under the conditions of the decarboxylation.

***cis*-4-*tert*-Butylcyclohexanoic Acid (2).** A mixture of 2 and 3 was treated with CH_2N_2 as described above. The methyl esters were separated by preparative glpc (10 ft × 0.38 in., 25% Carbowax 20M on Chromosorb P, 60–80 mesh, 160°, He flow 55 ml/min). The trans isomer had the longer retention time. To 6 ml of concentrated H_2SO_4 was added 0.673 g (314 mmol) of the pure methyl ester of 2. After 6 min, the reaction mixture was poured into ice–water,

and extracted with three 25-ml portions of diethyl ether. The combined ethereal extracts were extracted with three portions of 25 ml of saturated $NaHCO_3$. The combined $NaHCO_3$ extracts were acidified at 0° with 6 *M* HCl, and the precipitate (0.154 g) was removed by filtration. The filtrate was saturated with NaCl and extracted twice with 25-ml portions of diethyl ether. Drying the combined ether extracts over anhydrous $MgSO_4$, and concentration on the rotary evaporator, gave an additional 0.037 g of product, making the total yield 0.191 g (30.7%). Recrystallization from benzene gave crystals, mp 117–118° (lit.[11] 117.5–118°).

***trans*-4-*tert*-Butylcyclohexanoic Acid (3).** Hydrolysis of 0.565 g (2.85 mmol) of the pure methyl ester of **3** by the procedure described for the methyl ester of **2** gave 0.202 g (35.4%) of **3**, mp 173–174° (lit.[11] 174–175°).

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

Registry No.—**1**, 53783-19-0; **2**, 943-28-2; **3**, 943-29-3; 4-*tert*-butylbenzoic acid, 98-73-7; 4-*tert*-butyl-1,5-cyclohexadien-1-oic acid, 31673-51-5; *cis*-1-carbomethoxy-4-*tert*-butylcyclohexanoic acid, 53783-20-3; *trans*-1-carbomethoxy-4-*tert*-butylcyclohexanoic acid, 53783-21-4.

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1,6-Methano[10]annulene *via* a Solvolytic Pathway

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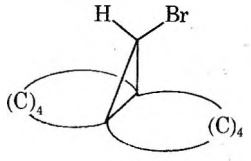
Received September 30, 1974

We and others have recently reported on the chemistry of various tricyclic dihalocyclopropanes.[1-8] Continued interest in this area has led us to study monohalo tricyclic systems of the general type **1**. We now wish to report on the chemistry of 11-bromotricyclo[4.4.1.$0^{1,6}$]undeca-3,8-diene (**2**). When **2** is treated with methanolic silver nitrate at



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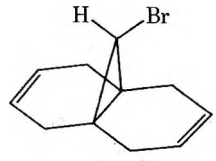
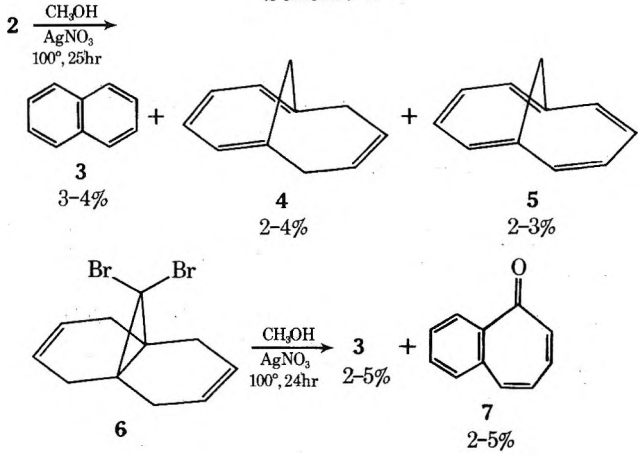


2

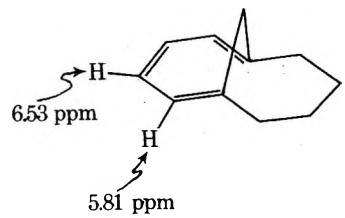
100°, three volatile products are obtained in a combined absolute yield of approximately 10% (Scheme I). The remaining, nonvolatile reaction product consists of apparently polymeric, intractable material from which we have not been able to isolate characterizable material by the usual separation techniques.

Scheme I



Compound **3** was readily identified as naphthalene by comparison of its nmr and infrared spectra with authentic material. The nmr spectrum of **5** was identical in all respects with that of the 1,6-methano[10]annulene published by Vogel.[9]

The structure of the tetraene **4** was assigned based on spectral data.[10a] The nmr of **4** exhibits absorption at 0.68 ppm (J = 9 Hz, 1 proton), 2.63 ppm (J = 9 Hz, 1 proton), 2.75–3.15 ppm (complex absorption, 4 protons), 5.32 ppm (broad singlet, 2 protons), 5.77 ppm (broad singlet, 2 protons), and 6.62 ppm (doublet of doublets, 2 protons). The low-field absorptions at 5.77 and 6.62 ppm are virtually identical in line shape and nearly identical in field position with the low-field absorptions reported by Vogel for the triene **8**.[10b,11]



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While the volatile products obtained from **2** are quite different from those obtained from **6**, the rates of silver ion assisted solvolysis are similar (Table I).

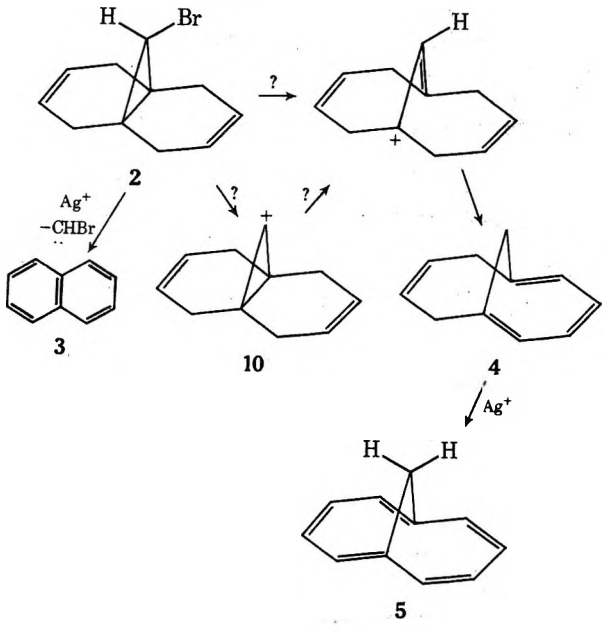
If one assumes that the rate-determining step in the solvolysis of each compound is the formation of a cyclopropyl cation, then any difference in rate between the two compounds should be a reflection of the difference in ground-state energy between the two. Implicit in this argument is the assumption that the cyclopropyl cation is planar and the further assumption that the effect of the α-bromo sub-

Table I[a]
Rate Constants and Activation Parameters of the Ag^+-Assisted Solvolysis of 2 and 6

Compd	Temp,[c] °C	k, l. mol^{-1} sec^{-1}	k_{rel} (25°)	ΔH^*, kcal/mol	ΔS^*, eu
2	140	1.89×10^{-3} (±0.02)			
	124	5.03×10^{-4} (±0.06)	1	27.6	−4.7
	25	3.12×10^{-9} [b]			
6[8]	25	6.97×10^{-9} [b]	2.2	30.3	5.7

[a] Silver perchlorate (~20-fold excess) in 95% methanol was employed in all solvolyses. [b] This is an extrapolated value. [c] At least two runs were made at each temperature.

Scheme II



stituent on the stability of the cyclopropyl cation formed from **6** will be negligible.[12,13]

One might thus expect to observe a larger difference in rate between **2** and **6** since the larger bromine substituent should increase the ground-state energy of **6** due to increased steric strain. In fact molecular mechanics indicate a difference in ground-state strain energy between **2** and **6** of 3.78 kcal/mol. This would correspond to a relative rate $k_6/k_2 = 600$.[14] However, it is risky to put too much faith in the absolute difference in strain energy between compounds of this type calculated in this manner.[15]

In addition, the low yields of isolable products preclude an unambiguous interpretation of the rate and product data. We offer a mechanistic scheme (Scheme II) as a suggested mode for the formation of **3–5**. Whether or not a cyclopropyl cation (*e.g.*, **10**) is in fact an intermediate in the solvolysis of **2** awaits further experimentation.[16]

Experimental Section[17]

11-Bromotricyclo[4.4.1.0^{1,6}]undeca-3,8-diene (2). To a refluxing solution of compound **6** (7.9 g, 0.026 mol) and a small amount of AIBN in 125 ml of absolute ether was added dropwise with stirring and under a nitrogen atmosphere 7.6 g (0.33 mol) of tri-*n*-butyltin hydride dissolved in 8 ml of absolute ether. After the addition was complete (2 hr) the reaction mixture was refluxed an additional 5 hr and then stirred at room temperature for 18 hr. The solvent was removed under reduced pressure and the resulting solution was then distilled. The fraction boiling between 90 and 100° (0.5 mm) was collected and then sublimed. Recrystallization of the sublimate from methanol afforded 3 g (56%) of material, mp 50–51° (lit.[18] mp 51°). The nmr spectrum of **2** was identical with that reported by Paquette.[19]

Silver Ion Assisted Methanolysis of 2. Compound **2** (3.0 g, 0.013 mol) and silver nitrate (22.5 g, 0.13 mol) were dissolved in 100 ml of methanol and heated for 25 hr at 100° in a glass pressure flask. After the usual work-up the crude reaction mixture was subjected to gas chromatographic analysis on an 8 ft × ¼ in. Hi-EFF (DEGS) 15% column. Three major components (**3–5**) were shown to be present. These were collected and identified (see text).[20] The absolute yields of **3–5** were determined using standard gas chromatographic techniques. α-Methylnaphthalene was employed as the internal standard.

Kinetic procedures as previously outlined[8] were employed. Eight points were taken for each run and 1,3-diphenylpropane was employed as an internal standard.

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—**2**, 4622-37-1; **4**, 38795-15-2; **5**, 2443-46-1; **6**, 4578-96-5.

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(10) (a) All attempts to free the sample of naphthalene met with no success. The spectra reported contain ~10% naphthalene as an impurity. This precluded a correct elemental analysis for compound **4**. (b) E. Vogel, *et al.*, *Justus Liebigs Ann. Chem.*, **759**, 1 (1972).
(11) The infrared spectrum of **4** exhibits absorption at 1630, 1597, and 1490 cm^{-1}, while **8** has absorption at 1494 and 1600 cm^{-1}.[10]
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(14) We thank Professor Paul Schleyer and Diane Khoury for performing the force field calculations mentioned above.
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(16) In a typical run for 25 hr at 100° the ratio of **4**:**3** was 1. However, when the reaction was carried out at 90° for approximately 15 hr, the ratio of **4**:**3** was 5. Starting material was still present and no detectable amounts of **5** were observed. Vogel has studied the thermal behavior of **4** extensively.[9] He has demonstrated that **4** is stable at temperatures below 250°. At temperatures above 250° **4** rearranges exclusively to benzocycloheptatriene. It thus seems unlikely that **4** is converted to **3** at 100°.
(17) Infrared spectra were determined with a Perkin-Elmer 457 recording spectrophotometer. The nmr spectra were measured at 60 MHz with an Hitachi Perkin-Elmer R20 spectrometer using tetramethylsilane as the internal reference. All spectra were measured in CCl_4 unless otherwise stated. A Hewlett-Packard 5750B gas chromatograph was used for all vpc analyses. All peak areas were integrated with a planimeter. Magnesium sulfate was employed as the drying agent. All reactions involving air- or moisture-sensitive compounds were carried out under a nitrogen atmosphere.
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Steroids and Related Natural Products. 90. 15β-Hydroxydigitoxigenin[1]

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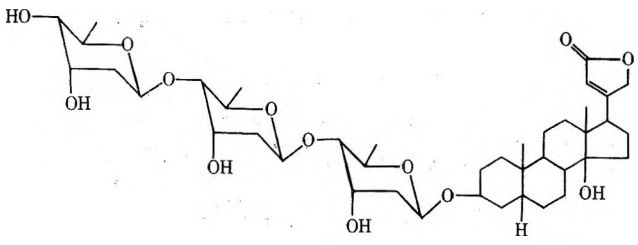
Biologically active steroids of the cardenolide type generally occur in plants[2] as glycosides and have also been isolated from butterflies[2] and toad venoms.[3] Isolation of the parent aglycone by acid hydrolysis of the corresponding glycoside is most useful with sugar attachments of the 2-deoxy type (*cf.* ref 1). If the aglycone is bound to a 2-hydroxy sugar such as D-glucose, acid hydrolysis is much less practical. In such cases enzymatic hydrolysis is considerably more useful.[4] One of the earliest procedures for acid-catalyzed cleavage of cardiac glycosides utilized a mixture of hydrochloric acid in aqueous acetic acid.[5] Another early procedure was based on alcoholysis with 2% hydrogen chloride in methanol.[6] The Reichstein[7] modification of these methods utilized an equal volume mixture of 0.1 *N* sulfuric acid–methyl alcohol to hydrolyze odoroside A and we have



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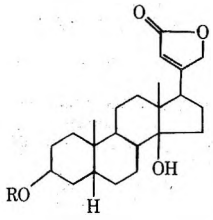
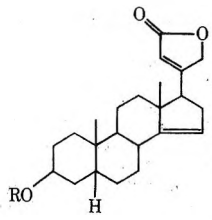
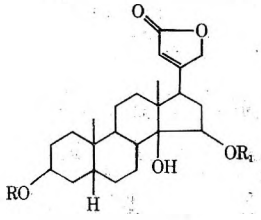


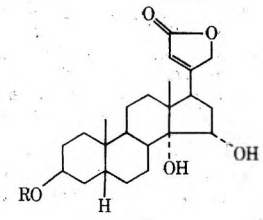
2a, R = H
b, R = $COCH_3$



3a, R = H
b, R = $COCH_3$



4a, R = R_1 = H
b, R = $COCH_3$; R_1 = H
c, R = R_1 = $COCH_3$



5a, R = H
b, R = $COCH_3$

routinely employed the same reagent for hydrolysis of digitoxin (1) to digitoxigenin (2a).[8]

The four-step (1 → 2a → 2b → 3b) conversion of digitoxin (1) to 3β-acetoxy-14-dehydrodigitoxigenin (3b) has been carried out many times in our laboratory.[1,9] Initially, we employed thionyl chloride in pyridine for dehydration of the tertiary alcohol 2b, but later concentrated hydrochloric acid in methanol (2 hr at reflux) was found more satisfactory.[10] Principal objectives of the present investigation involved finding a more efficient route for conversion of digitoxin (1) to olefin 3b and exploring Woodward[11] cis hydroxylation of the latter substance as a method of synthesizing 15β-hydroxydigitoxigenin (4a).[12] To begin with, digitoxin (1) was subjected to hydrolysis with concentrated hydrochloric acid in methanol. Brief warming led to a mixture of olefin 3a as major product accompanied by digitoxigenin (2a). By extending the reaction period to 90 min, good conversion to 14-dehydrodigitoxigenin (3a) as the only product was realized. Substitution of an acidic ion exchange resin for the hydrochloric acid gave digitoxigenin as major product accompanied by a lesser amount of olefin 3a.

Attention was next directed to one-step conversion of digitoxin to 3β-acetoxy-14-dehydrodigitoxigenin (3b). The most efficient method found involved heating glycoside 1 with *p*-toluenesulfonic acid in acetic acid–acetic anhydride. Good conversion to olefin 3b was routinely experienced and the presence of alcohol 2b was not detected. Shorter reaction periods gave either alcohol 2b or mixtures of both products (2b and 3b). The *p*-toluenesulfonic acid–acetic anhydride reagent also proved very effective for the transformation of diol 2a and alcohol 2b to olefin 3b.

Minimum reaction conditions necessary for partial dehydration of digitoxigenin (2a) and its acetate derivative (2b) to give a good yield of olefin 3a were also evaluated. Hydrochloric acid–methanol treatment[10] of digitoxigenin (2b) required 1 hr at reflux and with acetate 2b approximately 1.5 hr at reflux. In both cases good yields of olefin 3a were obtained. Extension of the reaction period to 2 hr and use of an acidic ion exchange resin in place of hydrochloric acid gave comparable yields of olefin 3a. As expected, both methods were quite suitable for transformation of acetate 3b to alcohol 3a. After completion of these model hydrolysis experiments and the practical procedure for one-step conversion of digitoxin to olefin 3b, the synthesis of 15β-hydroxydigitoxigenin (4a) was undertaken.

The very specific steric requirements of cis hydroxylation with osmium tetroxide would suggest that attack on olefin 3b would proceed from the less hindered α side and produce triol 5a. The very careful study of this reaction by Tamm[13] nicely showed α-side approach to be preferred. Formation of α-*cis*-diol 5a was favored over that of the β-*cis*-diol 4a in a ratio of 10:1. The lactone olefin system could also be hydroxylated by allowing diol 5a to react with osmium tetroxide. The stereochemistry of diols 4 and 5 was determined by degradation to the corresponding 17β-carboxylic acids and interpretation of spectral data.

In our hands osmium tetroxide hydroxylation of olefin 3b gave α-diol 5b as major product (42%) and only a minor amount (6.5%) of β-diol 4b. However, treatment of olefin 3b with iodine and silver acetate in aqueous acetic acid[11] afforded a good route to diacetate 4c. After purification by column chromatography and recrystallization, a 38% yield of the β product (4c) was recovered. Compelling evidence for structure 4c was provided by comparison with the diacetate obtained by acetylating the minor product (4b) of osmium tetroxide hydroxylation. Acid hydrolysis of acetate 4c at room temperature with, for example, hydrochloric acid in methanol completed the route to 15β-hydroxydigitoxigenin (4a).

Experimental Section[14]

Acid Hydrolysis of Digitoxin (1). Method A. With Hydrochloric Acid. A solution of digitoxin (1, 40 mg)[8] in methanol (1.4 ml) containing 35% hydrochloric acid (0.09 ml) was heated at reflux 90 min. The solution was poured into ice–water and extracted with chloroform and the solvent extract was washed with water and evaporated to dryness. The residue was subjected to column chromatography and the fraction eluted by 5:1 hexane–acetone was recrystallized from methanol–hexane to yield 16 mg of 14-dehydrodigitoxigenin (3a) melting at 199–202° (lit.[15,16] mp 198–204 and 202°).

With a 25-min period at reflux reaction of digitoxin (1, 80 mg) and 35% hydrochloric acid (0.18 ml) in methanol (2.8 ml) gave 30 mg of olefin 3a, mp 201–203°. A more polar fraction was recrystallized from 80% ethyl alcohol to yield 8 mg of digitoxigenin (2a) melting at 248–251°. Essentially the same yields of both products were obtained with ethyl alcohol as solvent.

Method B. With Amberlite CG-120 (H^+). A mixture prepared from digitoxin (1, 60 mg) in methanol (6 ml)–water (1.2 ml) and Amberlite CG-120 (H^+, 0.30 g) was heated at reflux for 1 hr. After filtration the solution was evaporated to a 47-mg residue which was purified as described in method A above to provide 8 mg, mp 200–202°, of olefin 3a and 14 mg, mp 250–252°, of digitoxigenin (2a). Substitution of Dowex-50W-X80 (H^+, 0.25 g) for the Amberlite resin led to 6 mg of olefin 3a and 14 mg of digitoxigenin.

Method C. With *p*-Toluenesulfonic Acid–Acetic Anhydride. A solution of digitoxin (1, 0.10 g) in acetic acid (5 ml)–acetic anhydride (1 ml) containing *p*-toluenesulfonic acid (50 mg) was allowed to remain at room temperature 7 hr. The crude product was isolated as noted in method A above except for washing the chloroform extract with dilute sodium bicarbonate. Recrystallization from acetone–hexane afforded 34 mg of olefin 3b melting at 182–184° (lit.[17] mp 182–183° and lit.[16] mp 192–193°). When the preceding reaction was terminated after 25 min, only 12 mg of 3β-acetoxydigitoxigenin (2b, mp 224–226° from acetone–hexane) was isolated. Substitution of acetic acid (5 ml) containing 5 drops of water for the acetic acid–acetic anhydride mixture and use of a 30-min period reflux led to 10 mg of olefin 3b, mp 183–185°, as the only hydrolysis product from 50 mg of digitoxin (1). The same reaction at room temperature with 0.10 g of digitoxin gave 21 mg, mp 249–251°, of digitoxigenin (2a) and 13 mg of olefin 3a melting at 198–202°.

The specimens of olefin 3b prepared by the above procedures

were found identical with a sample obtained by acetylating and dehydrating digitoxigenin (see following experiment).

3β-Acetoxy-5β-carda-14,20(22)-dienolide (3b). Method A. From Digitoxigenin. A solution of digitoxigenin (**2a**, 50 mg) and *p*-toluenesulfonic acid (5 mg) in acetic acid (2.5 ml) was heated at reflux for 30 min. The product **3b** was isolated as already outlined in the preceding experiment and found to weigh 46 mg and melt at 181–183° (after crystallization from methylene chloride–ethyl ether).

In another experiment digitoxigenin (**2a**, 50 mg) was allowed to react with the reagent prepared from *p*-toluenesulfonic acid (5 mg) and acetic acid (2.5 ml)–acetic anhydride (0.5 ml). The reaction was allowed to proceed at room temperature for 6 hr. After chromatographic purification of the product as described above, 44 mg of olefin **3b** (mp 181–184°) was isolated.

Method B. From 3β-Acetoxydigitoxigenin (2b). A solution of acetate **2b** (25 mg) and *p*-toluenesulfonic acid (2.5 mg) in acetic acid (6 ml) was allowed to remain at room temperature 6 hr. Olefin **3b** (21 mg, mp 180–183°) was isolated as just summarized.

14-Dehydrodigitoxigenin (3a). Method A. From Digitoxigenin (2a). Procedure 1. With Hydrochloric Acid. A solution composed of digitoxigenin (**2a**, 80 mg), 35% hydrochloric acid (0.18 ml), and either 3 ml of methanol or ethanol was heated at reflux 1 hr. Purification of the product by column chromatography and recrystallization of the product from methanol–hexane afforded 69 mg of olefin **3a** melting at 199–203°.

Procedure 2. With an Acidic Ion-Exchange Resin. The preceding dehyration reaction was repeated employing 30 mg of digitoxigenin in ethanol (3 ml)–water (0.6 ml) and either Amberlite CG-120 (H^+ form) or Dowex 50W-X80 (H^+ form). Here the period at reflux was 2 hr and 24 mg of olefin **3a** (mp 198–203°) was obtained.

Method B. From 3β-Acetoxydigitoxigenin (2b). The method A, procedure 1 (see above) hydrolysis reaction was repeated with acetate **2b** (0.10 g) and hydrochloric acid (2.2 ml) in ethanol (5 ml) at relux for 1.5 hr. After recrystallization the specimen of olefin **3a** amounted to 94 mg and melted at 200–204°.

When the preceding reaction was allowed to proceed only 25 min, a complex mixture of products resulted. The fractions eluted by 5:1 hexane–acetone were recrystallized to provide 28 mg of olefin **3b** (mp 182–185° from methylene chloride–ethyl ether), 54 mg of olefin **3a** (mp 199–203° from methanol–hexane), and 14 mg of digitoxigenin (mp 246–250° from methanol–hexane). The same mixture (16 mg of **3b**, 20 mg of **3a**, and 9 mg of **2a**) resulted from dehydrating 50 mg of digitoxigenin acetate (**2b**) with 0.25 g of Amberlite CG-120 (H^+ form). The reaction was conducted in methanol at reflux for 1 hr.

Acid-Catalyzed Hydrolysis of 3β-Acetoxy-5β-carda-14,20(22)-dienolide (3b). A solution of acetate **3b** (20 mg) in methanol (2 ml) containing 3 drops of water and 0.05 ml of 35% hydrochloric acid was heated at reflux 1 hr. After chromatographic purification and recrystallization, the yield of alcohol **3a** was 14 mg, mp 198–202°. Substitution of 0.10 g of Amberlite CG-120 (H^+ form) or the same amount of Dowex 50W-X80 (H^+ form) for the hydrochloric acid and extension of the reaction time to 2 hr led to 15 mg of alcohol **3a** melting at 199–201°.

Reaction of Osmium Tetroxide with 3β-Acetoxy-5β-carda-14,20(22)-dienolide (3a). The selective hydroxylation of olefin **3b** (0.5 g) was carried out with osmium tetroxide (0.5 g) in dry ethyl ether (70 ml)–pyridine (7 ml) during 8 hr (10°) essentially as described by Tamm and coworkers.[13] In this experiment the product was purified by column chromatography on silica gel. Elution with 3:1 hexane–acetone gave a mixture (0.26 g) of diols **4b** and **5b**. Rechromatography and elution with 5:1 hexane–acetone led (after recrystallization) to 34 mg of β-diol **4b** (mp 253–255° from methanol, lit.[13] mp 250–259°) and 0.21 g of α-diol **5b** (mp 201–203° from methanol, lit.[13] mp 202–203°).

3β,15β-Diacetoxy-14β-hydroxy-5β-card-20,22-enolide (4c, 15β-Hydroxydigitoxigenin Diacetate). Iodine (0.4 g) and silver acetate (0.4 g) were added to a solution of olefin **3b** (0.2 g) in acetic acid (12 ml)–water (0.6 ml). The mixture was stirred at room temperature 12 hr and the solution was filtered. Solvent was removed and the yellow residual solid was subjected to column chromatography. The fraction eluted by 9:1 hexane–acetone was recrystallized from methanol–hexane to afford 76 mg of diacetate **4c** as needles melting at 125–128° (lit.[13] mp 123–130°): λ_{max} 218 nm (log ε 4.21); ν_{max} 3580 (OH), 1780, 1740, 1728, 1620 (butenolide ring and ester CO), 1240, 1220 cm^{-1} (C–O); pmr (10% solution in deuteriochloroform) δ 0.94 (3 H, s, 18-CH_3), 0.96 (3 H, s, 19-CH_3), 2.05 (3 H, s, 3-OAc), 2.09 (5 H, s, 15-OAc), 2.77 (1 H, d, J = 7 Hz, 17-H), 4.8 and 5.1 (2 H, a narrow AB-type quartet, J = 2 Hz, 22-H); mass spectrum *m/e* 474 (M^+), 456 ($M^+ - H_2O$), 414 (M^+ – AcOH), 396 ($M^+ - H_2O$ – AcOH), 354 (M^+ – 2AcOH), 336 (M^+ – 2AcOH – H_2O).

Anal. Calcd for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.45; H, 8.09.

A 20-mg sample of diol **4b** was acetylated with acetic anhydride (0.3 ml)–pyridine (0.5 ml) at room temperature during 20 hr. The resulting diacetate **4c** was recrystallized from methanol–hexane to afford needles weighing 16 mg and melting at 123–127°. Diacetate **4c** originating from the osmium tetroxide approach was found identical with the product **4c** obtained by the iodine–silver acetate method.

15β-Hydroxydigitoxigenin (4a, 3β,14β,15β-Trihydroxy-5β-card-20(22)-enolide). A solution of diacetate **4c** (50 mg) in 80% ethanol (30 ml) containing sulfuric acid (0.2 ml) was allowed to stand at room temperature 3–5 days. The solution was poured into water, neutralized with dilute sodium bicarbonate, and extracted with chloroform. The combined extract was washed with water and the solvent was removed. The residue (46 mg) was chromatographed on a column of silica gel and a fraction eluted with hexane–acetone (3:1) was recrystallized from acetone–hexane to afford 28 mg of diol **4a** melting at 247–250° (lit.[13] mp 248–252 and 245–247°): λ_{max} 218 nm (log ε 4.20); ν_{max} 3540, 3480 (OH), 1780, 1745, 1625 cm^{-1} (butenolide ring); pmr (10% solution in deuteriochloroform) δ 0.91 (3 H, s, 18-CH_3), 0.97 (3, H, s, 19-CH_3), 2.78 (1 H, d, J = 7 Hz, 17-H), 4.10 (1 H, broad peak, 3α-H), 4.8 and 5.1 (2 H, a narrow AB-type quartet, J = 2 and 17 Hz, 21-CH_2), 5.88 (1 H, d, J = 2 Hz, 22-H); mass spectrum *m/e* 390 (M^+), 372 ($M^+ - H_2O$), 354 ($M^+ - 2H_2O$).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.89; H, 8.76.

The preceding reaction was repeated employing diacetate **4c** (25 mg) in 80% ethanol (30 ml) or methanol containing 35% hydrochloric acid (0.15 ml). The yield of triol **4a** melting at 245–248° was 14 mg. The yield of 15β-hydroxydigitoxigenin (**4a**) was slightly lowered by employing the acidic ion exchange resin method. For example, stirring diacetate **4c** (25 mg) in 80% ethanol (15 ml) with 0.125 g of Amberlite CG-120 (H^+ form) or Dowex 50W-X80 (H^+ form) for 5 hr at 45° gave 13 mg of triol **4a** melting at 245–249°.

Acknowledgments. We gratefully acknowledge support of this investigation by Public Health Research Grant No. CA-16049-01 from the National Cancer Institute. We also wish to thank the J. W. Kieckhefer Foundation, the Fannie E. Rippel Foundation, the Salt River Project of Arizona, The Arizona Public Service Co., and Mrs. Virginia L. Bayless for financial assistance.

Registry No.—**1**, 71-63-6; **2a**, 143-62-4; **2b**, 808-19-5; **3a**, 4321-20-4; **3b**, 4240-51-1; **4a**, 13265-07-1; **4c**, 35596-51-1.

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Reactions of 3,4-Benzopyrrolidinones with β-Keto Esters

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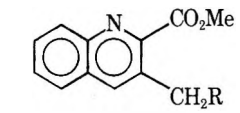
Received October 15, 1974

As part of a synthetic study directed toward camptothecin and camptothecin analogs,[1,2] we had occasion to synthesize the tricyclic lactam **1** and to investigate its utility as a starting material for various annelation schemes.[3] Our route to lactam **1**, which we believe to be simpler than the three[4–6] which have been described in the interim, is set forth below.

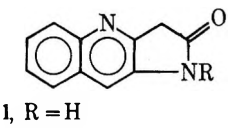
The required 2-carbomethoxy-3-methylquinoline (**2**) was prepared by the Friedlander condensation of 2-oxobutyric acid with o-aminobenzaldehyde followed by esterification of the intermediate acid[7] with methanolic HCl. Compound **2** (87%) was treated with *N*-bromosuccinimide and dibenzoyl peroxide in carbon tetrachloride. The intermediate 2-carbomethoxy-3-bromomethylquinoline (**3**), assumed to be present but not characterized, was treated with ammonia to give an 86% yield of **1**. This method[8] was extended to the preparation of phthalimidine (**5**). Treatment of methyl o-toluate with *N*-bromosuccinimide gave methyl-2-bromomethylbenzoate (**4**). Reaction of **4** with ammonia gave **5** in 60% yield.

Sugasawa had reported that heating of **1** with diethyl acetone-1,3-dicarboxylate (**6**) gave the acylated product **7**[9] in 95% yield. Before the experimental procedure became available, we attempted to achieve this result, based on our reading of the preliminary report,[9] by heating **1** + **6** at 160–165° at atmospheric pressure. No product corresponding to **7** was isolated. In fact, the starting material, **1**, was recovered largely unchanged.[10] However, when the actual experimental conditions of Sugasawa[6,11] (**1** + **6** (excess), 160–165° (15–20 mm)) were employed, a 94% yield of **7** was obtained. The reason for the dramatic effect achieved by conducting the reacton under vacuum is not clearly understood.

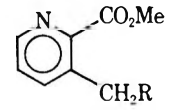
When the reactants **5** + **6** were heated neat at 160–165° for 2 hr at atmospheric pressure, a 77% yield of a crystalline product, mp 138–139°, was obtained. Both its mass spectrum and combustion analysis indicated it to be a product corresponding to **5** + **6** − H_2O. This information, in addition to that obtained from its nmr spectrum, defines its structure as the enamide **8**,[12] rather than the expected **9**.



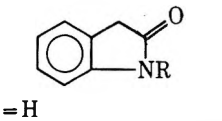
2, R = H
3, R = Br



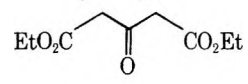
1, R = H
7, R = $COCH_2COCH_2CO_2Et$



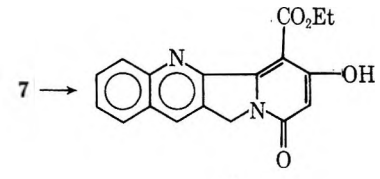
4



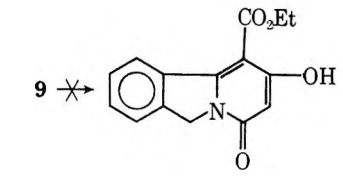
5, R = H
8, R = $(EtO_2CCH_2)C{=}C(H)CO_2Et$
9, R = $COCH_2COCH_2CO_2Et$
10, R = $(Me)C{=}C(H)CO_2Me$



6



11



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When the reaction of **5** + **6** was carried out under the Sugasawa conditions (15–20 mm, 160–165°, 0.5 hr), a mixture of **8** (24%) and another crystalline product, mp 94–95° (59%), was obtained. The mass spectrum and combustion analysis of the compound melting from 94 to 95° establish it to be the product of **5** + **6** − C_2H_6O. These data plus its nmr spectrum define its structure to be imide **9**, *i.e.* the analog of **7**.

Similarly, reaction of **5** with methyl acetoacetate at 200° for 18 hr gave a 46% yield of the crystalline enamide **10**,[11] mp 120–121°, whereas comparable conditions involving heating **1** with methyl acetoacetate up to 200–210° for 24 hr gave essentially recovered starting material and decomposition products. Also, Sugasawa had reported that cyclodehydration of **7** (formation of **11**) could be achieved (89%) using piperidine in acetonitrile. We were able to achieve the same result for compund **7**. However, attempts to extend the reaction to imide **9**, in the phthalimidine series (attempted formation of **12**), led to recovered starting material.

The greater nucleophilicity of the lactam nitrogen of **5** relative to **1** (enamide formation from β-keto esters *vs.* no reaction at atmospheric pressure) correlates logically with the greater electrophilicity of the carbonyl group of **7** relative to **9** with respect to internal aldolization (*cf.* **7** → **11**; **9** → **12**). Both presumably arise from the electron-withdrawing effect of the quinoline (inductive effect plus formal α-azomethine linkage) ring. The effect of the vacuum conditions in promoting imide relative to enamine formations is not understood.

The results of further studies involving annelations of **1** will be described shortly.

Experimental Section[13]

Preparation of 2-Carbomethoxy-3-methylquinoline (2). A solution of 2-oxobutyric acid (7.5 g; 0.074 mol), o-aminobenzalde-

hyde (8.0 g; 0.066 mol), and sodium methoxide (6.32 g; 0.117 mol) in 300 ml of methanol was heated under reflux for 12 hr. After cooling, 11.96 g (0.12 mol) of concentrated H_2SO_4 was cautiously added. The resultant solution was heated under reflux for 24 hr. After neutralization with aqueous sodium bicarbonate, the mixture was extracted with chloroform. After removal of the volatiles at the water pump, the residue was distilled at 0.01 mm. A fraction of bp 138–140° consisting of 11.54 g (87%) was obtained: λ_{max} (CCl_4) 5.79 μ; δ (CCl_4) 2.35 (s, 3), 3.78 (s, 3), 7–8 (m, 5).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.69. Found: C, 71.40; H, 5.63; N, 6.86.

Preparation of 3-Oxo-1*H*-pyrrolo[3,4-*b*]quinoline (1). A solution of **2** (19.51 g; 0.097 mol) in 50 ml of carbon tetrachloride was added, with stirring, to a solution of *N*-bromosuccinimide (17.05 g; 0.096 mol) and dibenzoyl peroxide (1.09 g; 0.0045 mol) in 200 ml of the same solvent. The temperature was raised over 1 hr to the boiling point and heating under reflux was continued for an additional 18 hr. After removal of the succinimide (lighter than the solvent) by filtration, the volatiles were evaporated at the water pump. The residual bromomethyl compound, **3**, was dissolved in 500 ml of methanol. Gaseous ammonia was continuously bubbled through the solution as concentrated ammonium hydroxide (9 drops) was added. Heating under reflux was continued for 2.5 hr. A white solid separated and was collected by filtration. Additional solid was obtained by concentration of the methanolic solution. Recrystallization of the combined solids from 95% ethanol yielded 15.28 g (86%) of compound **1**: mp 295–302° dec (lit.[6] 280–283° dec; λ_{max} (nujol) 3.05, 5.91μ; δ (CF_3CO_2H) 5.17 (s, 2), 8.3–9.2 (m, 4), 9.96 (s, 1), 10.04 (s, 1).

Anal. Calcd for $C_{11}H_{18}N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.49; H, 4.39; N, 14.99.

Conversion of Methyl *o*-Toluate to Phthalimidine (5). A mixture prepared by adding *N*-bromosuccinimide (114 g; 0.64 mol) and dibenzoyl peroxide (1.29 g; 5 mmol) to a solution of methyl *o*-toluate (90 g; 0.66 mol) in 350 ml of carbon tetrachloride was heated under reflux for 4 hr. After cooling and filtration of the succinimide, the solvent was evaporated at the water pump. The residue (125 g) consisting of **4** was dissolved in 500 ml of methanol. To this was added 150 ml of concentrated ammonia and the system was brought to reflux. Anhydrous ammonia was bubbled through. After cooling, the volatiles were removed at the water pump. The solid residue was washed with water and then with ether. The phthalimidine (48 g, 60%) upon recrystallization from water had a melting point of 155–156° (lit.[14] 150–151°).

Condensation of Phthalimidine (5) with Diethyl Acetone-1,3-dicarboxylate (6). (i) At Atmospheric Pressure (Formation of 8). Compound **5** (500 mg; 4.2 mmol) was added to excess (6 ml) **6**. The system was heated at 160–165° for 2 hr. On cooling, white crystals separated and were collected. More product was recovered by chromatography of the mother liquor on 300 g of silica gel by elution with 1:1 ether–petroleum ether. The elution order was **6** > **8** > **5**. The combined solid, **8**, mp 138–139°, weighed 923 mg (77% conversion; 93% yield). In addition compound **5** (100 mg; 20%) was recovered: *m/e* 317 (parent); λ_{max} ($CHCl_3$) 5.80, 5.89 (sh), 6.18 (sh), 6.20 μ; δ ($CDCl_3$) 1.25 (t, J = 7 Hz, 6 H, overlapping triplets), 4.20, 4.22 (2 q, J = 7 Hz for each, 4 H), 4.68 + 4.70 (2 s, 4 H), 5.65 (s, 1 H), 7.2–8.0 (m, 4 H).

Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.35; H, 5.99; N, 4.44. Found: C, 64.36; H, 6.07; N, 4.40.

(ii) **At Reduced Pressure (Formation of 8 + 9).** Phthalimidine (**5**) (1.0 g; 7.55 mmol) was added to an excess 12 ml of **6**. The system was connected to an aspirator (15–20 mm). It was heated at 160–165° for 30 min. After cooling the total mixture was chromatographed on *ca.* 600 g of silica gel. Elution with 1:1 ether–petroleum ether first removed **6**. After this, 0.56 g (23%) of **8** was obtained. The final product eluted was compound **9**: 1.28 g (59% yield); mp 94–95°; *m/e* 289 (parent); λ_{max} ($CHCl_3$) 5.80 (sh) 5.85, 5.92 (sh), 6.20 μ; δ ($CDCl_3$)[15] 1.30 (t, J = 7 Hz, 3 H), 3.72 (s, 2 H), 4.05–4.40 (q, J = 7 Hz, + s δ = 4.3, total = 4 H), 4.83 (s, 2 H), 7.3–8.0 (m, 4 H).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.19; N, 4.84. Found: C, 62.57; H, 5.15; N, 4.75.

Reaction of 5 with Methyl Acetoacetate. Formation of 10. Phthalimidine (500 mg; 3.7 mmol) and methyl acetoacetate (1 g; 8.5 mmol) were heated in a sealed tube at 200° for 18 hr. After cooling, the contents were dissolved in chloroform. Addition of petroleum ether gave a precipitate which was recrystallized from ethanol to give **10**: 410 mg; 46% yield; mp 120–122°; *m/e* 231 (parent); λ_{max} 5.80, 5.85, 6.20 μ; δ ($CDCl_3$) 2.76 (s, 3 H), 3.70 (s, 3 H), 4.55 (s, 2 H), 5.95 (s, 1 H), 7.2–8.0 (m, 4 H).

Acknowledgments. This research was supported by Public Health Service Grant No. CA-12107-05-10. Nmr spectra were obtained on facilities supported by Public Health Service Grant No. RR-00292-05. Preliminary studies in the phthalimidine series were conducted by Dr. Lantz Crawley.

Registry No.—**1**, 34535-42-7; **2**, 53821-46-8; **5**, 480-91-1; **6**, 105-50-0; **8**, 53821-47-9; **9**, 53821-48-0; **10**, 53821-49-1; 2-oxobutyric acid, 600-18-0; o-aminobenzaldehyde, 529-23-7; *N*-bromosuccinimide, 128-08-5; methyl *o*-toluate, 89-71-4; methyl acetoacetate, 105-45-3.

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(10) Although starting **1** was recovered in high yield (starting with 368 mg, 320 were recovered) the mass spectrum of the mother liquors exhibits a small peak at *m/e* 368 which corresponds to 1 + 6 − H_2O, *i.e.*, the enamide analog of **7**. Thus, there may be a slight amount of enamine formation even here.
(11) We thank Dr. Sugasawa for making the details of his excellent procedure available to us prior to publication.
(12) The double bond geometry is unspecified.
(13) Melting points are uncorrected. Nmr spectra were measured at 60 MHz on Varian Associates A60, A60D, and T60 spectrometers with tetramethylsilane as internal standard. Data are reported in parts per million (δ) from TMS. Infrared spectra were obtained from Perkin-Elmer 137 or 247 spectrophotometers. Mass spectra were measured on an LKB 9 combined glc–mass spectrometer by direct insertion. Analyses were conducted by Galbraith Inc., Knoxville, Tenn.
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(15) The nmr spectrum also indicates the presence of *ca.* 20% of enol tautomers.

Synthesis of Benziodathiazoles

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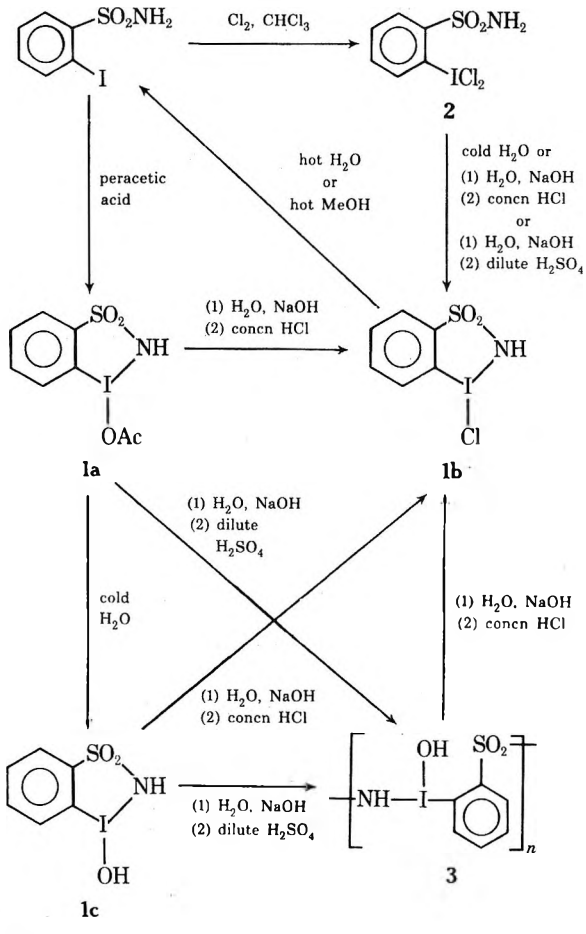
Received October 7, 1974

A number of heterocyclic compounds whose rings contain polyvalent iodine have been described. Recently we have reported on the synthesis and properties of *o*-iodosophenylphosphoric acid and its methyl ester to which we have assigned the six-membered cyclic structures 1,3-dihydroxy-1*H*-1,2,4,3-benziodadioxaphosphorin 3-oxide and 1-methoxy-3-hydroxy-1*H*-1,2,4,3-benziodadioxyphosphorin-3-oxide.[2]

The present note describes the synthesis of polyvalent iodine derivatives of *o*-iodobenzenesulfonamide to which we have assigned the five-membered benziodathiazole structures **1a–c**. Entry into the benziodathiazole system is achieved *via* 1-acetoxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1a**) (Scheme I) synthesized by peracetic acid oxidation of *o*-iodobenzenesulfonamide or *via* 1-chloro-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1b**) synthesized by hydrolysis of *o*-(dichlorido)iodosobenzenesulfonamide (**2**). The latter is synthesized by chlorination of o-iodobenzensulfonamide. Compound **1b** is also obtained by acidification of a NaOH solution of **1a** or **2** (Scheme I).

Scheme I



Hydrolysis of **1a** gives 1-hydroxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1c**). Acidification of a NaOH solution of **1a** or **1c** with sulfuric acid gives an insoluble white powder (**3**) which is probably a polymeric form of **1c**.

Benziodathiazoles **1a–c** and the polymer **3** are interconvertable as shown in Scheme I. In addition both **1b** and **3** can be regenerated from their NaOH solutions by acidification (Scheme I).

Treatment of **1b** with boiling methanol or water results in the reduction of its polyvalent iodine function to give *o*-iodobenzenesulfonamide.

Structures were assigned mainly on the basis of ir and pmr spectra rather than elementary analyses. The latter suffer from poor reproducibility of the analyses of NSI or NSICl compounds as well as the instability of some of the compounds.

Spectroscopic Properties of 1b. The ir spectrum of **1b** has S=O stretch bands at 1345 and 1160 cm^{-1} and sharp N–H stretch peaks at 3352 and 3249 cm^{-1}.

The nmr spectrum in DMSO-d_6 has a broad D_2O-exchangeable signal for the NH proton. The two protons ortho to sulfur and iodine appear downfield from the other aromatic protons as a multiplet approximating two triplets at τ 1.87 and 1.99, respectively. The position of the signal from the proton ortho to I is consistent with a covalent structure rather than an ionic one such as $>I^+Cl^-$. For example, the proton ortho to positively charged iodine in 3-butyl-2-phenylbenziodolium chloride[4] gives a signal much further downfield at τ 1.05.

Spectroscopic Properties of 1a. The broad bands at 3199 and 3134 cm^{-1} and the band in the low carbonyl region (1624 cm^{-1}) in the infrared spectrum of **1a** would be consistent with either the >I–O acetyl and N–H structure shown or an N acetyl and >I–OH structure.[5-7]

However, the nmr spectrum of **1a** in DMSO-d_6 displays a methyl singlet at τ 8.09 and aromatic absorption at τ 2.90–1.39. Underlying the latter is a D_2O-exchangeable absorption attributed to the NH group occurring in the same region observed for this and similar groups in the spectra of **1b**, **1c**, **3**, and *o*-iodobenzenesulfonamide. The absence of any upfield OH absorption as in the spectra of **1c** and **3** excludes the 2-acetyl structure.

Spectroscopic Properties of 1c and 3. The ir spectrum of 1-hydroxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1c**) displays a single NH band at 3266 cm^{-1} and broad OH absorption with maxima at 3154 and 3082 cm^{-1}.

Compound **3** has broad bands in the ir corresponding for the most part to an envelope of the ir bands of **1c**. The nmr spectrum of **3** is essentially identical to that of **1c** except for a downfield shift of the OH peak. Analytical data suggest an empirical formula $C_6H_6INO_3S$.

Experimental Section

Sodium o-iodobenzenesulfonate hydrate was made from diazotized orthanilic acid and KI by the general procedure of Vogel.[8] The product appeared on the basis of nmr to contain about 1.4 mol of water. It was converted to the acid chloride by reaction with $POCl_3$, and then into the amide.[9]

o-(Dichlorido)iodosobenzenesulfonamide (2). A stirred solution of 0.75 (.0026 mol) of *o*-iodobenzenesulfonamide in 200 ml of dry $CHCl_3$ was chilled in an ice bath and treated with dry chlorine for 1 hr. The yellow precipitate that had formed after several minutes was filtered, washed with carbon tetrachloride, and dried to give 0.88 g (98%) of *o*-(dichlorido)iodosobenzenesulfonamide (**2**) as a yellow powder. Storage in the freezer prevented decomposition. Analysis of **2** was not attempted, but its color and solubility are typical of iodosodichlorides.

1-Acetoxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-Dioxide (1a). A suspension of 12.0 g (.0424 mol) of *o*-iodobenzenesulfonamide in 28 ml of 40% peracetic acid was vigorously stirred until after *ca.* 4 hr a clear yellow solution resulted. Stirring was continued for an additional 21 hr during which a thick white suspension gradually formed. Filtration and thorough drying at high vacuum gave 11.5 g (80%) of 1-acetoxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1a**) as a white solid: mp 146–147° dec to red oil with gas evolution (tube in at 145°, heated at 1–2°/min); ir (Nujol and Fluorolube) 3199 (NH), 3134 (NH), 3086, 3057, 2985 (CH_3), 2934 (CH_3), 1624 (C=O), 1593, 1560, 1436, 1371, 1359, 1320 (S=O), 1309 (S=O), 1294, 1218, 1169 (S=O), 1159 (S=O), 1127, 1099, 1007, 930, 869, 799, 773, 766, 735, 709, 696, 674, 663, and 647 cm^{-1}; nmr (DMSO-d_6) τ 1.83–2.52 (m, 5, aromatic H and NH [D_2O exchangeable]) and 8.09 (s, 3, OAc).

Anal.[10] Calcd for $C_8H_8INO_4S$: C, 28.17; H, 2.36; S, 9.40; equivalent wt, 170.5. Found: C, 26.83; H, 1.90; S, 10.01; equivalent wt, 166.4 (iodometric).

1-Chloro-1,2-dihydro-1,3,2-benziodathiazole 3,3-Dioxide (1b). To a vigorously stirred fresh solution of 2.00 g (0.00587 mol) of 1-acetoxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1a**) in 20 ml of 1 *N* NaOH was added dropwise an excess of concentrated HCl. The resulting yellow precipitate was filtered, air dried on the filter, and pumped at high vacuum to give 1.79 g (96%) of 1-chloro-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1b**) as a yellow solid: mp 105–106° dec with gas evolution (tube in at 105° and heated at 1–2°/min); ir (Nujol and Fluorolube) 3352 (NH), 3249 (NH), 3084, 3072, 1568, 1560, 1442, 1429, 1345 (S=O), 1336 (S=O), 1278, 1260, 1183, 1160 (S=O), 1133, 1120, 1103, 1043, 1032, 1019, 989, 914, 819, 773, 764, 735, 703, 694, 682, and 647 cm^{-1}; nmr (DMSO-d_6) τ 1.78–2.08 (m approximating two triplets centered at 1.87 and 1.99, 2, protons ortho to iodine and sulfur), 2.26–2.97 (m, 2, other aromatic H), *ca.* 1.03–2.67 (broad, 1, NH, exchangeable with D_2O).

Anal. Calcd for $C_6H_5ClINO_2S$: C, 22.69; H, 1.59; S, 10.10; equivalent wt, 158.7. Found: C, 23.01; H, 1.35; S, 10.20; equivalent wt, 162.1 (iodometric).

This compound with identical ir spectrum was also obtained in 80% yield by hydrolysis of **2** in water or in NaOH followed by neutralization with either H_2O or H_2SO_4.

1-Hydroxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-Dioxide (1c). A suspension of 2.00 g (.00587 mol) of 1-acetoxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1a**) in 40 ml of water was vigorously stirred for 16 hr. Filtration, washing sparingly with water,

and thorough drying at high vacuum gave 1.69 g (96%) of 1-hydroxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide as a white solid: mp 146° explodes (tube in at 145° and heated at 1–2°/min); ir (Nujol and Fluorolube) 3266 (NH), 3134 (OH), 3082 (OH), 1556, 1439, 1319, 1309 (S=O), 1241, 1181, 1167 (S=O), 1159 (S=O), 1140, 1126, 1112, 1099, 1083, 1116, 1006, 934, 898, 852, 784, 770, 750, 734, 700, 669, and 645 cm^{-1}; nmr (DMSO-d_6) τ 1.82–2.56 (m, 5, aromatic H and HN [D_2O exchangeable]) and 6.68 (broad, 1, OH, D_2O exchangeable).

Anal.[10] Calcd for $C_6H_6INO_3S$: C, 24.09; H, 2.02; S, 10.72; equivalent wt, 149.5. Found: C, 25.21; H, 1.79; S, 10.71; equivalent wt, 145.9 (iodometric).

Compound 3. Method A. To a vigorously stirred solution of 0.50 g (0.0015 mol) of 1-acetoxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1a**) in 2.5 ml of 1 *N* NaOH was added excess dilute H_2SO_4 dropwise. The resulting precipitate was filtered, washed with cold water, and dried in high vacuum to give 0.38 g (87%) of a pale yellow solid (**3**): mp 147° explodes (tube in at 145° and heated at 1–2°/min); ir (Nujol and Fluorolube) 3504 (br), 3104 (br), 3080 (br), 1630 (br), 1555, 1435, 1293 (br), 1153, 1124, 1094, 1031, 1009, 893 (br), 766, 735, and 703 cm^{-1}, nmr (DMSO-d_6) τ 1.83–2.56 (m, 5, aromatic H and NH [D_2O exchangeable]) and 4.69 (br, 1, OH, D_2O exchangeable).

Anal.[10] Calcd for $C_6H_6INO_3S$: C, 24.09; H, 2.02; S, 10.72; equivalent wt, 149.5. Found: C, 24.63; H, 1.57; S, 11.77; equivalent wt, 151.8 (iodometric).

Method B. To a vigorously stirred solution of 0.50 g (0.0017 mol) of 1-hydroxy-1,2-dihydro-1,3,2-benziodathiazole 3,3-dioxide (**1c**) in 5 ml of 1 *N* NaOH was added dropwise excess dilute H_2SO_4. The resulting precipitate was filtered, washed with cold water, and dried under high vacuum to give 0.33 g (66%) of **3** with identical ir.

Conversion of 1c to 1b. To a vigorously stirred solution of 0.50 g (0.0017 mol) of **1c** in 10 ml of 1 *N* NaOH was added dropwise concentrated HCl. The resulting precipitate was filtered, washed with cold water, and dried under vacuum to give 0.50 g (94%) of **1b**.

Conversion of 3 to 1b. To a vigorously stirred solution of 0.50 g (0.0017 mol) of **3** in 3.0 ml of 1 *N* NaOH was added excess concentrated HCl, dropwise. The resulting precipitate was filtered, washed with cold water, and dried under vacuum to give 0.43 g (81%) of **1b**.

Regeneration of 1b. To a vigorously stirred solution of 0.25 g (0.00079 mol) of **1b** in 5.0 ml of 1 *N* NaOH was added dropwise excess concentrated HCl. The resulting gummy precipitate was triturated in the mother liquor to give a granular precipitate. Filtration, washing sparingly with cold water, and drying under vacuum gave 0.20 g (80%) of **1b** with unchanged ir.

Regeneration of 3. To a vigorously stirred solution of 0.20 g (0.00067 mol) of **3** in 2.0 ml of 1 *N* NaOH was added dropwise excess dilute H_2SO_4. The resulting precipitate was filtered, washed with cold water, and dried under vacuum to give 0.08 g (40%) of **3** with unchanged ir.

Reduction of 1b in Refluxing Methanol. A suspension of 0.30 g (0.00095 mol) of **1b** in 2.0 ml of anhydrous methanol was refluxed for 5 min to give a yellow solution with a sharp odor. Upon cooling 0.10 g (37%) of *o*-iodobenzenesulfonamide was deposited.

Reduction of 1b in Hot Water. A suspension of 0.50 g (0.00150 mol) of **1b** in 15 ml of water was boiled for 10 min to give a pale yellow solution with a sharp odor. Upon cooling 0.20 g (46%) *o*-iodobenzenesulfonamide (identified by ir) was deposited.

Registry No.—**1a**, 53730-93-1; **1a** polymer, 53730-94-2; **1b**, 53730-97-5; **1c**, 53730-95-3; **1c** polymer, 53730-96-4; **2**, 53730-98-6; **3**, 53730-92-0; *o*-iodobenzenesulfonamide, 53730-99-7.

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Synthesis of 3,4,5-Tris(aryl- and alkylthio)-2,6-pyridinedicarbonitriles

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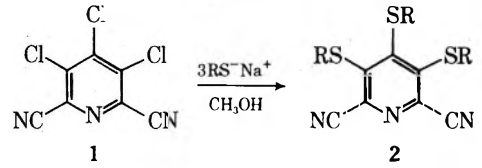
Received November 11, 1974

Although aromatic, nucleophilic displacements are well known for pentachloropyridine[2] and related halogenated pyridines, multiple displacements are often difficult and slow. In this note we describe the reaction of 3,4,5-trichloro-2,6-pyridinedicarbonitrile (**1**),[3] in which all three chlorines are activated toward nucleophilic aromatic substitution, with 3 equiv of a sodium thiolate in methanol at room temperature to afford the corresponding 3,4,5-tris(aryl- or alkylthio)-2,6-pyridinedicarbonitrile (**2**, eq 1, Table I). The reaction is extremely rapid, beginning as soon as



1 2 (1)

the reactants are mixed. It appears that once one thio group is introduced, the remaining two chlorines are very rapidly replaced as evidenced by the isolation of 3,4,5-tris(methylthio)-2,6-pyridinedicarbonitrile (**2**, R = CH_3) from the reaction of **1** with 1 equiv of sodium methanethiolate.

Table I
3,4,5-Tris(aryl- and alkylthio)-2,6-pyridinedicarbonitriles (2)

R	Mp, °C	Yield, %	Registry no.
CH_3	98–100	90	35646-45-8
C_6H_5	125–127	94	53862-54-7
4-$CH_3C_6H_4$	189–190	91	53862-55-8
4-$(CH_3)_3CC_6H_4$	150–152	48	53862-56-9
4-BrC_6H_4	158–160	92	53862-57-0
2-$C_{10}H_7$	165–167	67	53862-58-1

The structure of **2**, R = CH_3, and hence that of the entire series, was confirmed by its carbon-13 NMR spectrum (Table II), which is clearly indicative of the symmetrical nature of the molecule. The 100-MHz proton spectrum of **2**, R = CH_3 displays singlets at δ 2.62 and 2.70, in a ratio of 1:2, which further confirms the symmetry of the molecule and substantiates the presence of methylthio groups in different environments in a ratio of 1:2.

Table II
^{13}C NMR of 2, R = CH_3

	Chemical shift, δ [a]
C_2 and C_6	156.9
C_4	146.0
C_3 and C_5	134.4
C≡N	114.8
CH_3S	19.3

[a] Recorded in parts per million downfield from tetramethylsilane.

Experimental Section[4]

3,4,5-Tris(aryl- and alkylthio)-2,6-pyridinedicarbonitriles. In a 500-ml, single-neck flask equipped with a magnetic stirrer and

a reflux condenser fitted with a calcium chloride drying tube were placed 300 ml of methanol and 2.76 g (0.12 g-atom) of sodium metal. After all of the sodium had reacted, 0.12 mol of thiol was added and the resulting solution was stirred for 15 min. To the thiolate solution, 9.28 g (0.04 mol) of 3,4,5-trichloro-2,6-pyridinedicarbonitrile was added. The solution immediately became yellow in color, and a slight exotherm was observed. After stirring for several minutes, the contents of the flask solidified to a bright yellow, solid mass. The solid was filtered off and vacuum dried. The solid was recrystallized from methylene chloride–hexane or ethanol when necessary.

Reaction of 1 with 1 Equiv of Sodium Methanethiolate. In a 1-l., three-neck flask equipped with a magnetic stirrer, a rubber septum, and a reflux condenser fitted with a calcium chloride drying tube were placed 600 ml of methanol and 2.30 g (0.10 g-atom) of sodium metal. After all of the sodium had reacted, 6 ml of methanethiol (*stench*) was added to the methanol solution. The solution was allowed to stir for 0.5 hr, and then 23.25 g (0.10 mol) of 3,4,5-trichloro-2,6-pyridinedicarbonitrile was added. The reaction mixture immediately became yellow in color. The reaction mixture was heated to reflux (to make the system homogeneous) and then allowed to cool slowly to room temperature. Flat, white crystals separated which were filtered and dried to give 9.50 g of recovered 3,4,5-trichloro-2,6-pyridinedicarbonitrile, mp 198–200°. The methanol was removed from the filtrate in vacuo, leaving, after vacuum drying, 12.77 g of a pale yellow solid. The solid was treated with 100 ml of boiling 95% ethanol, and the resulting yellow solution was filtered. Upon cooling, long, bright yellow needles separated. The crystallization liquor was decanted, and the remaining needles were recrystallized from 50 ml of 95% ethanol to give, after vacuum drying, 0.78 g of 3,4,5-tris(methylthio)-2,6-pyridinedicarbonitrile (**2**, R = CH_3), mp 98–100°. Cooling the previously decanted crystallization liquor (see above) gave an additional 0.33 g, mp 98–100°.

Registry No.—**1**, 17824-85-0; sodium methanethiolate, 5188-07-8; sodium benzenethiolate, 930-69-8; sodium 4-methylbenzenethiolate, 10486-08-5; sodium 4-*tert*-butylbenzenethiolate, 5787-50-8; sodium 4-bromobenzenethiolate, 13457-82-4; sodium 2-naphthalenethiolate, 875-83-2.

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(4) All melting points are uncorrected. All new compounds gave satisfactory elemental analyses and ir and NMR spectra. The 100-MHz proton spectra were recorded on a Varian HA-100 spectrometer with an internal lock on tetramethylsilane. The carbon-13 spectrum was recorded at 25.2 MHz on a Varian XL-100-15 spectrometer equipped with a Digilab NMR-3 Fourier transform system.

A Convenient Preparation of Unsymmetrically Substituted Pyrroles, Furans, and Thiophenes

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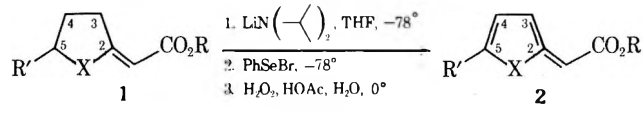
Received October 15, 1974

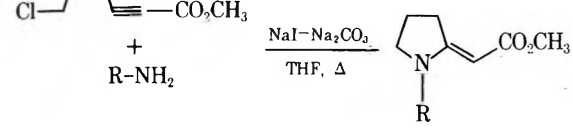
We wish to report a facile and versatile synthesis of substituted pyrroles, furans, and thiophenes. During one phase of a study of conjugated enamines,[1] we have found that enamino esters (**1a** and **1b**), enol ether esters (**1c**), or thioenol ether esters (**1d**) undergo γ-alkylation with benzeneselenenyl bromide. Oxidation (H_2O_2) and elimination of benzeneseleninic acid, followed by in situ double bond isomerization, afforded pyrrole (**2a** or **2b**), furan (**2c**), or thiophene (**2d**) in good yield.



	% yield
a, X = N—$(CH_2)_2$—$C_6H_3(OCH_3)_2$; R = CH_3; R′ = H	**2a**, 86
b, X = N—$(CH_2)_5CO_2CH_3$; R = CH_3; R′ = H	**2b**, 71
c, X = O; R = CH_2CH_3; R′ = CH_3	**2c**, 94
d, X = S; R = CH_2CH_3; R′ = CH_3	**2d**, 95

Spectral analyses of the products were consistent with the proposed structures.[2] The most notable change in going from **1** to **2** was the disappearance of vinyl absorptions in the ^1H NMR spectra of **1** and appearance of low-field methylene singlets in **2**. Also, disappearance of aliphatic ring proton absorptions of **1** and appearances of low-field multiplets characteristic of pyrroles, furans, and thiophenes were consistent with the assigned product. The infrared and ultraviolet spectra also showed absorption changes characteristic of conjugated esters being converted to unconjugated esters.[3]

The utility of this facile conversion is further supported by the ease of preparation of the enamino esters. For example, **1b** was prepared by concomitant Michael addition–alkylation of methyl 6-aminohexanoate with methyl 6-chloro-2-hexynoate in the presence of sodium iodide and sodium carbonate. Overnight reflux under nitrogen in THF



typically gave an 85% yield of enamino ester on work-up. Benzylamine, butylamine, phenethylamines, and ammonia have also been used in this process (70–95%).

Similarly, the relative simplicity of the preparation of **1c** and **1d** by epoxide or sulfide ring opening with the dianion of ethyl acetoacetate allows for the synthesis of a variety of tetrahydrofurylidene acetates and tetrahydrothiophenylidene acetates, and consequently a variety of furans and thiophenes, respectively.[4] The γ-alkylation of enamino esters[1] coupled with this aromatization sequence should give 3-substituted pyrroles.[5]

It is interesting to note that in this work we have not found evidence for sulfur oxidation in the oxidation–elimination sequence. This seems to confirm other qualitative reports of the relative ease of selenium oxidation compared to that of sulfur.[6]

Experimental Section[7]

Methyl *N*-(5-Carbomethoxypentyl)-α-pyrrolidinylideneacetate (1b). Methyl 6-chloro-2-hexynoate (3.13 g), methyl 6-aminohexanoate (3.00 g), sodium iodide (3.75 g), and sodium carbonate (2.65 g) were added to tetrahydrofuran (anhydrous, 60 ml) and refluxed for 20 hr under an atmosphere of nitrogen. After cooling, the reaction mixture was poured into water (100 ml) and methylene chloride (100 ml). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 50 ml). The combined organic extracts were washed with aqueous sodium chloride (saturated, 50 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give 5.55 g of crude product. Chromatography on alumina (50 g, Woelm activity grade III) with chloroform gave 5.25 g (100%) of **1b**: λ_{max} (film) 2950, 2860, 1735 (s), 1680 (s), 1595 (vs), 1435, 1140 (vs), 1060, and 780 cm^{-1}; δ_{TMS} ($CDCl_3$) 4.50 (t, J = 1.5 Hz, vinyl), 3.66 (s, 3 H, methoxyl), 3.59 (s, 3 H, methoxyl), 3.37 (t, J = 7 Hz, 2 H, C_5 H's), 3.15 (t, J = 7 Hz, 4 H, C_3 H's and NCH_2C), 2.31 (t, J = 7 Hz, 2 H, $-CH_2CO_2-$), 1.2–2.2 (m, 8

H, C_4 H's and $NCCH_2CH_2CH_2CCO_2$); λ_{max} (EtOH) 287 nm; *m/e* 269.

Methyl *N*-(β-3,4-Dimethoxyphenethyl)-α-pyrrolidinylideneacetate (1a). Using the procedure described above, methyl 6-chloro-2-hexynoate (3.00 g), sodium iodide (3.00 g), sodium carbonate (anhydrous, 2.12 g), and 3,4-dimethoxyphenethylamine (3.60 g) afforded **1a** (4.04 g, 71%) which was recrystallized from methanol–water (mp 90–100°): λ_{max} (CH_2Cl_2) 1670, 1590 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.72 (m, 3 H, phenyl), 4.54 (s, 1 H, vinyl), 3.85 (s, 6 H, methoxyl), 3.62 (s, 3 H, methyl ester), 3.40 (m, 6 H, C_5 H's and phenethyl H's), 2.88 (m, 2 H, C_3 H's), and 1.85 (m, 2 H, C_4 H's); λ_{max} (EtOH) 290 nm; *m/e* 305.

Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59. Found: C, 66.88; H, 7.61.

General Procedure. To a solution of lithium diisopropylamide (1.1 equiv prepared from diisopropylamine and 1.8 *M* butyllithium in hexane) in 100 ml of anhydrous THF prepared under a nitrogen atmosphere at −78° was added the unsaturated ester in 3 ml of THF (dropwise). The solution was allowed to warm to 0° before cooling to −78° and rapidly adding benzeneselenenyl bromide (1.1 equiv, prepared by adding 0.55 equiv of bromine to 0.55 equiv of diphenyl diselenide in 3 ml of THF).[8] The solution was warmed to 0° and water, acetic acid, and 30% hydrogen peroxide were added rapidly. In all cases the reaction temperature was maintained below 25° until gas evolution ceased (30–60 min). The solution was poured into saturated sodium bicarbonate and extracted with methylene chloride. The combined extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), concentrated in vacuo, and purified as indicated below.

***N*-(β-3,4-Dimethoxyphenethyl)-2-carbomethoxymethylpyrrole (2a).** Chromatography of crude product [prepared as described above from **1a** (0.50 g)] on silica gel with 5% THF–$CHCl_3$ gave 0.43 g (86%) of **2a:** λ_{max} (CH_2Cl_2) 3050 (w), 3000 (w), 2955, 1740, 1725, 1710, 1640, 1515, 1235, 1150, and 1030 cm^{-1}; δ_{TMS} ($CDCl_3$) 8.13 (d, *J* = 6 Hz, 1 H, C_5 H), 6.67–6.83 (m, 3 H, phenyl), 6.28 (dd, *J* = 6, 1.5 Hz, 1 H, C_4 H), 5.48 (m, 1 H, C_3 H), 3.83 (s, 9 H, carbomethoxyl and methoxyl), 3.75 (s, 2 H, $-CH_2CO_2-$), 3.73 (t, *J* = 8 Hz, 2 H, NCH_2C), 2.77 (t, *J* = 8 Hz, 2 H, benzylic); *m/e* 303.

***N*-(5-Carbomethoxypentyl)-2-carbomethoxymethylpyrrole (2b).** Alkylation and aromatization of **1b** (0.38 g) gave 0.27 g (71%) of **2b** (oil), purified by chromatography on silica gel: λ_{max} (CH_2Cl_2) 3030, 2950, 1735, 1730, 1610, 1420, 1125, and 1040 cm^{-1}; δ_{TMS} ($CDCl_3$) 8.11 (d, *J* = 6 Hz, 1 H, C_5 H), 6.30 (dd, *J* = 6 Hz, 1 H, C_4 H), 5.57 (m, 1 H, C_3 H), 3.60–3.95 (m, 10 H, $-CO_2CH_3$, $-CO_2CH_3$, NCH_2C, and $-CH_2CO_2$), 2.30 (m, 2 H, $-CH_2CH_2CO_2$), and 1.1–1.7 [m, 6 H, $-(CH_2)_3-$]; λ_{max} (EtOH) 270 nm.

2-(Carboethoxymethyl)-5-methylfuran (2c). Alkylation and aromatization of **1c** (1.7 g) gave 1.58 g (94%) as a light yellow liquid (unstable in air): λ_{max} (film) 3010, 2950, 1745, 1700, 1640, 1380, 1120, and 1045 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.07 (m, 1 , C_4 H), 5.92 (m, 1 H, C_3 H), 4.12 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 3.60 (s, 2 H, $-CH_2CO_2$), 2.23 (s, 3 H, C_5 methyl), and 1.21 (t, *J* = 7.2 Hz, 3, H, $-CH_2CH_3$); *m/e* 168; λ_{max} EtOH) 223 nm.

2-(Carboethoxymethyl)-5-methylthiophene (2d). Alkylation and aromatization of **1d** (0.93 g) gave an oil (0.88 g) which was chromatographed on silica gel with 10% ethyl acetate–chloroform to give 0.76 g (81%) of **2d:** λ_{max} (film) 2950, 2920, 2870, 1740, 1695, 1580, 1185 (s), and 1040 cm^{-1}; δ_{TMS} ($CDCl_3$) 7.40 (m, 1 H, C_4 H), 6.60 (m, 1 H, C_3 H), 4.13 (q, *J* = 7 Hz, 2 H, OCH_2CH_3), 3.70 (s, 2 H, $-CH_2CO_2$), 2.40 (s, 3 H, C_5 methyl), 1.28 (t, *J* = 7 Hz, 3 H, $-CH_2CH_3$); *m/e* 184; λ_{max} (EtOH) 242 nm.

Acknowledgment. We gratefull acknowledge the Research Corporation for support of this work.

Registry No.—**1a,** 53906-86-8; **1b,** 53906-87-9; **1c,** 40954-15-2; **1d,** 40954-17-4; **2a,** 53906-88-0; **2b,** 53906-89-1; **2c,** 53906-90-4; **2d,** 53906-91-5; methyl 6-chloro-2-hexynoate, 51804-12-7; methyl 6-aminohexanoate, 2780-89-4; 3,4-dimethoxyphenethylamine, 120-20-7.

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(1) R. B. Gammill and T. A. Bryson, *Tetrahedron Lett.*, 3963 (1974).
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(3) In no case did the ester side chain of **1b** interfere with the γ-alkylation of the extended enolate (e.g., proton transfer, acylation, Michael-like addition to enamino ester).
(4) T. A. Bryson, *J. Org. Chem.*, **38,** 3428 (1973).
(5) (a) G. Wittig, R. Roderer, and S. Fischer, *Tetrahedron Lett.*, 3517 (1973); (b) T. A. Narwid and A. I. Meyers, *J. Org. Chem.*, **39,** 2574 (1974).
(6) See ref 8a and references cited therein.
(7) For the spectral properties of compounds **1c** and **1d,** see ref 5, for the spectral properties of compound **1a,** see ref 1.
(8) (a) H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95,** 5813 (1973); (b) *J. Org. Chem.*, **39,** 2133 (1974).

Rearrangement of Allylic Phosphonates

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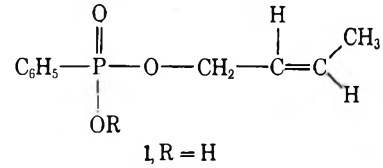
Received September 23, 1974

Allylic phosphates and pyrophosphates are key intermediates in the biosynthesis of terpenoids, steroids, and many other natural products. In view of the extensive studies on such systems and the intense current interest in head-to-head processes such as the farnesyl pyrophosphate → squalene conversion,[1] it is surprising that no example of an allylic isomerization of a phosphate, phosphonate, or phosphinate has been reported. Solvolysis of linaloyl phosphate in 70% aqueous acetone gave no detectable internal return to geranyl and neryl phosphates.[2] In the spontaneous decomposition of geranyl and neryl diphenyl phosphates in ether, linaloyl diphenyl phosphate was suggested as an intermediate, but could not be detected.[3] Finally, a labeled allyl diphenylphosphinate showed no scrambling of the allyl group at 220°.[4] We wish to report a simple system in which allylic isomerization is facile and some evidence which suggests the mechanism of the rearrangement.

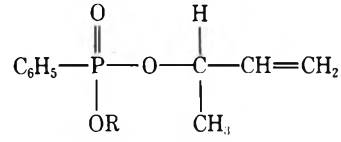
The compounds selected for study were crotyl phenylphosphonate (**1**) and α-methylallyl phenylphosphonate (**2**). The monoesters were obtained from the reaction of phenylphosphonodichloridate with 1 equiv of the corresponding alcohol, followed by aqueous work-up. The oily products could not be distilled, but were purified by an extraction sequence. Samples slowly deteriorated at room temperature, but could be stored for months at −10° without decomposition.

The interconversion of **1** and **2** was effected by heating a 10% solution of either compound in chlorobenzene or nitrobenzene. The isomerization was conveniently monitored by NMR; the methyl doublet of **2** occurs about 0.27 ppm upfield from the complex methyl region of the cis–trans mixture of **1**. The equilibration was accompanied by some decomposition, but equilibrium could be approached from either side. The equilibrium mixture in nitrobenzene at 80° is ca. 30:70, favoring the more substituted double bond in **1**.

The following experiments[5] are pertinent to the mechanism of the rearrangement. (1) The rate of isomerization is concentration dependent, becoming faster at higher concentrations. (2) The rearrangement is completely inhibited by pyridine, but is accelerated by trifluoroacetic acid. (3)



1, R = H
3, R = CH_3



2, R = H
4, R = CH_3

The reaction is ca. 2.5 times faster in nitrobenzene than in chlorobenzene under similar conditions. (4) Rearrangement cannot be observed in hydroxylic solvents; rather, the allylic group is cleaved. (5) The α-methylallyl methyl ester **4** undergoes isomerization to the crotyl methyl ester **3** at 130°, but at a rate ca. 20 times slower than the isomerization of **2** to **1** at the same temperature and concentration; this reaction is accelerated by the free acid **2**.

One intriguing mechanistic possibility for the isomerization is a 3,3-sigmatropic shift. This pathway has been demonstrated in the isomerization of allylic thiophosphates in which the oxygen to sulfur migration is accompanied by inversion of the allylic group.[6] An allyl phosphinate was found not to undergo such Claisen-type rearrangements,[4] but a monoallyl phosphonate such as **2** bears a labile acidic proton. The more nucleophilic oxygens in the anion of **2** might be more prone to initiate the sigmatropic shift.

The data clearly eliminate this possibility, however; the inhibition by pyridine indicates that the anion is inert, while the concentration dependence and effect of trifluoroacetic acid require that the reactive species is either the neutral or protonated **2**.

An ionic mechanism involving C–O cleavage to produce allylic cations is completely consistent with the observations. In hydroxylic solvents, the cations are intercepted without internal return and no isomerization is observed. The rate increase in nitrobenzene over chlorobenzene also supports this conclusion. The function of acid may be merely to prevent ionization of the strong phosphonic acid; in this case the neutral acid **2** would dissociate to an ion pair.[7] The isomerization of the neutral methyl ester **4** under nonacidic conditions shows that such a pathway is likely. On the other hand, the much slower isomerization of **4** suggests that **2** may react in a protonated form to produce a neutral phosphonic acid and an allylic cation which then recombine; such a mechanism seems required for the acid catalysis of isomerization of **4**. Cleavage in both neutral and protonated forms has been suggested for dibenzyl phosphate[8] and it appears that both mechanisms occur with rather similar energies for the allylic esters under the conditions described herein.

It thus appears that ionic mechanisms direct the isomerization of allyl phosphonates even in chlorobenzene. The detection of this rearrangement is a special case in a nonnucleophilic solvent; the possible significance of such rearrangements in biological systems remains unknown.

Experimental Section

Preparation of 3-Buten-2-yl Phenylphosphonate (2). A solution of phenylphosphonodichloridate (19.5 g) and pyridine (19 g) in anhydrous ether (300 ml) was stirred in an ice bath under argon while 3-buten-2-ol (6.0 g) was added over 15 min. After warming to room temperature, the mixture was poured into ice water containing 4 g of NaOH. The organic layer was separated, extracted with bicarbonate, and discarded. The aqueous layer and bicarbonate extract were acidified to pH <1 with concentrated HCl and extracted thrice with 75 ml of chloroform. Evaporation of the chloroform extracts gave a colorless oil which was treated[9] with a solution of 12 g of barium hydroxide in 120 ml of water. Ethanol (100 ml) was added and the precipitate was removed. The filtrate was concentrated on a vacuum pump to about one-half the volume, then adjusted to pH <1 with concentrated HCl and extracted with ether (3 × 50 ml). The organic layers were combined, dried, and evaporated to give 7.4 g of a viscous oil.

Anal. Calcd for $C_{10}H_{13}O_3P$: C, 56.58; H, 6.18. Found: C, 56.31; H, 5.93.

The NMR ($CDCl_3$, Varian A-60A) showed complex multiplets centered at δ 7.7 (2 H) and 7.3 (3 H) (aromatic protons) and at 5.7 (1 H) and 5.0 ppm (3 H) (vinyl and methine protons) plus a doublet for the methyl group at 1.31 ppm.

The 2-buten-1-yl phenylphosphinate **1**, a known compound,[10] was prepared from crotyl alcohol by a similar procedure. Its NMR spectrum ($CDCl_3$) showed multiplets at 7.7 (2 H) and 7.3 (3 H) (aromatic protons), 5.57 (2 H) (vinyl) and 4.5 (2 H) (methylene), and a broad doublet at 1.58 ppm (3 H) for the methyl group.

Equilibrations. Weighed samples of **2** or **1** in a NMR tube were diluted with 0.60 ml of chlorobenzene or nitrobenzene and immersed in a constant-temperature bath at 79.9°. The samples were withdrawn and NMR spectra recorded at regular intervals. Effects of pyridine, D_2O, and trifluoroacetic acid were determined by adding a known amount of each to the initial sample.

On one occasion, to confirm that **1** was the product from **2**, the equilibrated sample after 15 hr in chlorobenzene at 80° was pumped to dryness on a vacuum pump and put through the extraction sequence described above in the preparation of **2**. The NMR remained that of a mixture of **1** plus **2**.

Methyl 3-Buten-2-yl Phenylphosphonate (4). A solution of phenylphosphonodichloridate (25.4 g), pyridine (21 g), and 300 ml of ether was stirred in an ice bath under argon while first methanol (4.5 g) and then 3-buten-2-ol (8 g) were added dropwise. The mixture was filtered and the filtrate was washed with bicarbonate, dried over $MgSO_4$, and evaporated to give 15 g of colorless oil. The oil was fractionated by Kugelrohr distillation to give 9 g of **3** at 130° (0.01 mm).

Anal. Calcd for $C_{11}H_{15}O_3P$: C, 58.38; H, 6.69. Found: C, 58.14; H, 6.60.

Registry No.—**1**, 53940-78-6; **2**, 53940-79-7; **3**, 53940-80-0; **4**, 53940-81-1; phenylphosphonodichloridate, 824-72-6.

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(2) W. Rittersdorf and F. Cramer, *Tetrahedron*, **24**, 43 (1968); **23**, 3015 (1967).
(3) R. C. Haley, J. A. Miller, and H. C. S. Wood, *J. Chem. Soc. C*, 264 (1969).
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(5) Most of these experiments were performed on both isomers, but the conversion of **2** into **1** proceeds to a greater extent and was examined more thoroughly. In view of the autocatalysis and the minor impurities in **2**, accurate kinetics were impractical and only qualitative rate trends are described.
(6) A. N. Pudovic and I. M. Aladzheva, *Zh. Obshch. Khim.*, **30**, 2617 (1960).
(7) B. K. Tidd, *J. Chem. Soc. B*, 1168 (1971).
(8) J. Kumamoto and F. Westheimer, *J. Am. Chem. Soc.*, **77**, 2515 (1955).
(9) The purification procedure is adapted from that of E. Cherbuliez, S. Colak-Antic, F. Hunkeler, and J. Rabinowitz, *Helv. Chim. Acta*, 1827 (1963).
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New Syntheses of Functional Arenesulfonyl Azides

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Received October 10, 1974

The synthesis of light-sensitive polymers containing sulfonyl azide groups requires functional monomers, which can be readily prepared from inexpensive starting materials. For the construction of these polymers two principles can be used: (a) reaction of an arenesulfonyl azide containing two functional groups with another difunctional monomer to produce addition or condensation polymers, and (b) reaction of a monofunctional arenesulfonyl azide with a multifunctional linear polymer. Mono-, as well as difunctional, arenesulfonyl azides were prior to our investigation virtually unknown.[1]

A readily available starting material for the synthesis of functional arenesulfonyl azides is 4-isocyanatobenzenesulfonyl chloride (**1**), which is obtained in high yield by phosgenation of sulfanilic acid.[4] In order to achieve a completely selective functionalization of **1**, it was treated with excess ethylene glycol or triols at room temperature in acetonitrile

Table I
Arenesulfonyl Azides

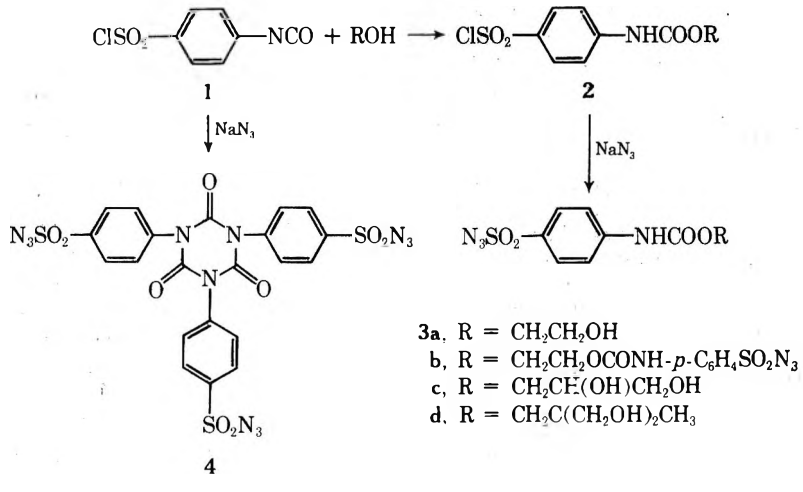
Compd	Arenesulfonyl azide	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N[c]
3a	N_3SO_2—C$_6$H$_4$—NHCOOCH$_2$CH$_2$OH	120–122	91	$C_9H_{10}N_4O_5S$	37.76	3.52	19.57	37.60	3.73	17.13
3b	$(N_3SO_2)_2$—C$_6$H$_3$—NHCOOCH$_2$)$_2$	170–172	45	$C_{16}H_{14}N_8O_8S_2$	37.65	2.75	21.96	37.45	2.82	20.92
3c	N_3SO_2—C$_6$H$_4$—NHCOOCH$_2$CH(OH)CH$_2$OH	121	72	$C_{10}H_{12}N_4O_6S_2$	37.97	3.80	17.72	37.69	4.04	16.74
3d	N_3SO_2—C$_6$H$_4$—NHCOOCH$_2$C(CH$_2$OH)$_2$CH$_3$	*a*	~100	$C_{12}H_{16}N_4O_6S$	41.86	4.68	16.27	41.58	4.51	15.82
4	$(N_3SO_2$—C$_6$H$_3$—NCO)$_3$	*b*	89	$C_{21}H_{12}N_{12}O_9S_3$	37.50	1.80	24.99	37.55	1.84	22.48

[a] Viscous liquid. [b] Decomposition at approximately 200° (see Table II). [c] Lower percentages of nitrogen were observed in the elemental analyses because of violent thermal decomposition.

to give the 2-hydroxyalkyl 4-chlorosulfonylcarbanilates (**2**) exclusively. Under the mild reaction conditions no reaction of the chlorosulfonyl group with the excess di- or triol is observed.

The progress of the reaction of **1** with the alcoholic hydroxyl group is monitored by infrared spectroscopy. After disappearance of the isocyanato group, sodium azide is added to the reaction mixture, which causes rapid conversion of **2** to give hydroxyalkyl 4-azidosulfonylcarbanilates (**3**). It is essential that all of the isocyanate has reacted prior to the addition of the sodium azide, because unreacted **1** is readily trimerized by the basic sodium azide. For example, treatment of **1** with sodium azide in acetonitrile at room temperature produces the novel tris(4-azidosulfonylbenzene)isocyanurate (**4**) exclusively (Scheme I).

Scheme I



Reaction of 2 equiv of **1** with ethylene glycol gives rise to the formation of the bis carbamate **3b** (see Table I). Attempts to achieve selective reaction of **1** with aliphatic amines failed, because there is not a sufficient differential in rates of reaction of amines with both functional groups in **1**. The infrared spectra of the carbanilates **3** show a SO_2N_3 stretching at 2083 cm^{-1} and a C=O stretching at 1739 cm^{-1}, while **4** shows a SO_2N_3 stretching at 2132 cm^{-1} and a C=O stretching at 1698 cm^{-1}.

Arenesulfonyl azides undergo photolytic and thermal degradation with evolution of nitrogen gas. All carbanilates **3** have defined melting points, but violent decomposition occurs at 180–200°. The isocyanurate **4** has no sharp melting point, and violent decomposition is observed at approximately 200°. The thermal decomposition temperature of all arenesulfonyl azides is somewhat dependent on the rate of heating (see Table II). The carbanilate monomer **3a** has been grafted to anhydride copolymers to give light-sensitive polycarboxylic acids.[5] In order to prepare light-sensitive polycarboxylic acids by a reverse scheme, i.e., reaction of an azidosulfonyl group containing anhydride with hydroxy group containing linear polymers, the novel 4-azidosulfonylphthalic anhydride (**7**) has been synthesized by the route outlined in Scheme II. The required precursor, 4-chlorosulfonylphthalic anhydride (**6**), is obtained by the reaction of 4-sulfophthalic anhydride (**5**) with phosphorus pentachloride. Reaction of **7** with hydroxy group containing polymers gives rise to the formation of light-sensitive polycarboxylic acids.[6]

Scheme II

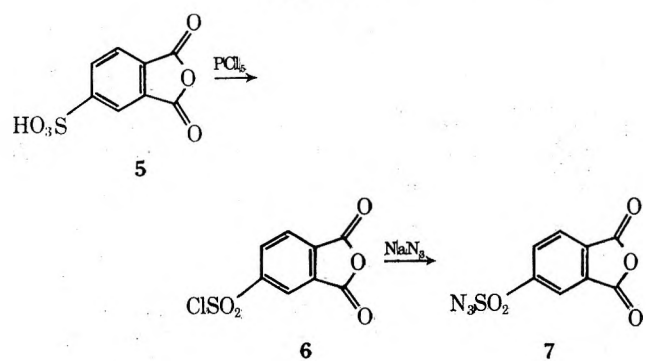


Table II
Thermal Decomposition of Arenesulfonyl Azides by Differential Scanning Calorimeter

Compd	T_m	T_d (40°/min)	T_d (80°/min)
3a	120–122	180	215
3b	170–172	192	212
3c	121	190	210
4		198	208

Experimental Section[7]

2-Hydroxyethyl 4-Azidosulfonylcarbanilate (3a). To an amount of 50.4 g (0.8 mol) of ethylene glycol in 500 ml of acetonitrile with cooling and stirring a solution of 43.2 g (0.2 mol) of 4-isocyanatobenzenesulfonyl chloride in 100 ml of acetonitrile was added over a period of 10 min at 2–8°. After disappearance of the N=C=O stretching in the infrared spectrum of the reaction mixture, 13 g (0.2 mol) of sodium azide was added and the reaction mixture was stirred at room temperature for 60 min. The precipitated sodium chloride was removed by filtration, and on evaporation of most of the solvent under vacuum and addition of water 52 g (91%) of 2-hydroxyethyl 4-sulfonylazidocarbanilate, mp 115–118°, was precipitated. Recrystallization from acetonitrile raises the melting point to 120–122°. The azidocarbanilates **3b–d** were prepared similarly.

Tris(4-azidosulfonylbenzene)isocyanurate (4). To 26 g (0.4 mol) of sodium azide suspended in 400 ml of acetonitrile a solution of 87 g (0.4 mol) of 4-isocyanatobenzenesulfonyl chloride[4] was added over a period of 20 min at 4–10°. After stirring at room temperature for 3 hr 600 ml of water was added to precipitate a mixture of product and sodium chloride, which was washed several times with water to remove the salt. Thus 79.7 g (89%) of 4 was obtained: mp ~200° (violent dec); ir (acetonitrile) 2132 (SO_2N_3), 1698 cm^{-1} (C=O).

4-Chlorosulfophthalic Anhydride (6). To 229.35 g (1.1 mol) of phosphorus pentachloride suspended in 1000 ml of acetonitrile, 228 g (1 mol) of 4-sulfophthalic anhydride (obtained from molten phthalic anhydride and sulfur trioxide) was added. The reaction mixture was refluxed for 150 min and the solvent was evaporated under vacuum. The residue was dissolved in 1000 ml of methylene chloride and washed twice with 300 ml of water. The organic layer was dried with magnesium sulfate, the solvent was evaporated, and vacuum distillation of the residue gave 163.2 g (66.2%) of 4-chlorosulfonylphthalic anhydride: bp 170° (0.5 mm); mp 91–92° (CCl_4); ir ($CHCl_3$) 1869, 1786 cm^{-1} (C=O).

Anal. Calcd for $C_8H_3ClO_5S$: C, 38.95; H, 1.22; Cl, 14.37. Found: C, 38,80; H. 1.53; Cl, 14.16.

4-Azidosulfonylphthalic Anhydride (7). To a solution of 12.3 g (0.05 mol) of 4-chlorosulfonylphthalic anhydride in 125 ml of acetonitrile, 3.25 g (0.05 mol) of sodium azide was added. After stirring for 4 hr at room temperature the precipitated sodium chloride was removed by filtration and the solvent was removed under vacuum. Trituration of the residue with diethyl ether gave 8.8 g (69.5%) of **7**: mp 93–94°; ir ($CHCl_3$) 2137 (SO_2N_3), 1869 and 1786 cm^{-1} (C=O).

Anal. Calcd for $C_8H_3N_3O_5S$: C, 37.94; H, 1.18; N, 16.60. Found: C, 38.27; H, 1.09; N, 16.23.

Registry No.—**1**, 6752-38-1; **3a**, 33780-21-1; **3b**, 34280-60-9; **3c**, 34235-62-6; **3d**, 34235-60-4; **4**, 31328-33-3; **5**, 134-08-7; **6**, 39871-41-5; **7**, 37696-57-4; ethylene glycol, 107-21-1; 1,2,3-propanetriol, 56-81-5; 2-(hydroxymethyl)-2-methyl-1,3-propanediol, 77-85-0; sodium azide, 26628-22-8.

References and Notes

(1) The use of isocyanatobenzenesulfonyl azides[2] and 3-sulfonylazidobenzoyl chloride[3] to graft onto hydroxy group containing linear polymers are the only reported examples.
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(4) L. M. Alberino, H. Ulrich, and A. A. R. Sayigh, *J. Polym. Sci., Part A*, **5**, 3212 (1967).
(5) F. A. Stuber, H. Ulrich, D. V. Rao, and A. A. R. Sayigh, *Photogr. Sci. Eng.*, **17**, 446 (1973).
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(7) Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn.; ir spectra were taken on a Beckman IR-8 spectrophotometer. All melting points (uncorrected) were determined on a Fisher-Johns apparatus.

Preparation and Anodic Peak Potentials of Salts of Coordination Compounds Derived from Boric Acid and Polyhydric Phenols

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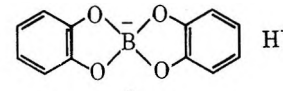
Received November 5, 1974

The coordination compounds derived from boric acid and dihydric phenols have the spiran structure shown in I,



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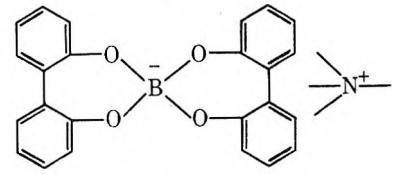

II

for the compound from boric acid and catechol. They have been studied since the late 19th century, and this work has been reviewed in a comprehensive manner by Steinberg.[1] Salts of these coordination compounds are now being used extensively as the solute in the electrolyte of electrolytic capacitors.[2] As a result we have had occasion to prepare the salts listed in Table I.

Alkali metal and amine salts have been reported previously,[1] but quaternary ammonium salts have been described only in the patent literature.[2] The bis-2,2′-dihydroxybiphenylborate salts are of special interest, since they have the structure, shown in II, where the spiran rings about the boron atom are seven-membered, and the four aromatic rings are very probably forced into two planes, one perpendicular to the other. These geometrical requirements, the seven-membered spiran rings and the largely planar configuration for the two biphenyl ring systems, do not result in any difficulty in the preparation of these salts, since they are readily obtained in high yield and are extremely stable once formed.

Peak potentials for the anodic oxidation of the free phenols and the salts were determined at a platinum anode by cyclic voltammetry at a scan rate of 200 mV/sec in dimethyl sulfoxide containing 0.1 *M* tetrabutylammonium fluoroborate as the supporting electrolyte. The results are shown in Table II. Since in each case studied there is no significant change in potential in going from the free phenol to the salt, the initial anodic process must be the same for both the free phenol and the salt and must consist of an electron transfer from an aromatic ring to form a cation radical. This must be true for the salts even though the negative charge is centered on the boron atom. It also follows that the change from free phenol to coordination compound is not accompanied by any significant perturbation of the electronic structure of the aromatic rings.

The current functions, $i_p/V^{1/2}C^*$, where i_p is the peak current, V is the scan rate, and C^* is the bulk concentration of the electroactive species, decreased with increasing scan rate. This is indicative of a chemical reaction coupled with the electron transfer. It is highly probable that catechol, 2,3-naphthalenediol, and 2,2′-dihydroxybiphenyl are electrochemically equivalent, since the observed current function values were similar. Catechol and 4-methylcatechol have been reported to undergo a two-electron oxidation coupled with a nucleophilic addition reaction.[3] The current function values for the complexes were consistently

Table I
Salts of Coordination Compounds Derived from Boric Acid and Dihydric Phenols

Registry no.	Cation	Yield, %	Mp, °C	N calcd	N found
	A. Biscatecholborate Salts				
53992-90-8	Dimethylammonium	86	325–350 dec	5.12	4.97
53992-91-9	Di-2-propylammonium	83.7	211–214	4.26	4.19
22364-89-2	Tetramethylammonium	83	290–291	4.65	4.50
53992-92-0	Tetraethylammonium	78	125–127	3.94	3.92
20234-44-0	Benzyltrimethylammonium	78	166–168	3.71	3.67
53992-93-1	*p*-Nitrobenzyltrimethylammonium	59.7	276–277	6.63	6.51
53992-95-3	*p*-Xylylene bis(triethylammonium)	87.6	222–225	3.68	3.61
	B. Bis-*p*-*tert*-butylcatecholborate Salts				
53992-97-5	Benzyltrimethylammonium	62.9	290–292	2.86	2.75
	C. Bis-2,3-naphthalenediolborate Salts				
53992-99-7	Tetramethylammonium	80.5	291 dec	3.49	3.27
53993-00-3	Benzyltrimethylammonium	67	257–259	2.93	2.91
53993-01-4	*p*-Nitrobenzyltrimethylammonium	82.6	318–319 dec	5.36	5.31
	D. Bis-2,2′-dihydroxybiphenylborate Salts				
53993-03-6	Dimethylammonium	85.6	260–262	3.29	3.07
53993-04-7	Di-2-propylammonium	86.1	317–321	2.91	2.92
53993-05-8	Tetramethylammonium	95	352–355	3.09	3.18
53993-06-9	Benzyltrimethylammonium	89	286–288	2.65	2.69

Table II
Peak Potentials for Anodic Oxidation of the Free Phenols and the Salts in Dimethyl Sulfoxide

Compd	E_p, V vs. Ag/Ag^+ (0.1 *M*)
Catechol	0.69
Dimethylammonium borodicatecholate	0.68
2,3-Naphthalenediol	0.80
Tetramethylammonium borodi(2,3-naphthalenediolate)	0.82
2,2′-Dihydroxybiphenyl	0.96
Benzyltrimethylammonium borodi(*o*,*o*′-biphenolate)	0.94

greater than those for the free phenols, and this may be attributed to either a difference in the diffusion rate or a difference in the rate of the coupled chemical reaction. The peak potentials also changed with scan rate, with the peak potentials increasing by approximately 100 mV when the scan rate was increased from 50 to 500 mV/sec.

Experimental Section

The salts were generally prepared by dissolving the dihydric phenol and amine or aqueous solution of a quaternary ammonium hydroxide in methanol. A solution of the requisite amount of boric acid in hot water was then added, and the resultant solution was distilled to dryness at the water pump. The crude product was then crystallized, most commonly from methanol–ether or acetone–ether. The preparation of tetramethylammonium borodicatecholate described below is typical.

Tetramethylammonium Borodicatecholate. Catechol (220.2 g, 2 mol) was mixed with 912 ml of 10% aqueous tetramethylammonium hydroxide, and methanol was added to complete solution. A solution of boric acid (61.8 g, 1 mol) in hot water was added, and the resultant solution was distilled at the water pump. The residue was crystallized from 2-propanol–methanol–ether to yield 250 g (83%) of the salt. A sample, recrystallized for analysis, had mp 290–291°.

Anal. Calcd for $C_{16}H_{20}BNO_4$: C, 63.81; H, 6.69; N, 4.65. Found: C, 64.03; H, 6.92; N, 4.50.

The dimethylammonium salts can be prepared as above, using dimethylamine, or, more simply, by heating a solution of the dihydric phenol and boric acid in the molar ratio of 2:1 in dimethylformamide at 125–130° for 24 hr.

Dimethylammonium Borodi(o,o′-biphenolate) A solution of 2,2′-dihydroxybiphenyl (9.3 g, 0.05 mol) and boric acid (1.55 g, 0.025 mol) in dimethylformamide (125 ml) was heated for 24 hr at 125–130°. Cooling and addition of ether gave 9.7 g (91.5%) of the salt, mp 258–261°, crystallized from dimethylformamide. As prepared in this manner the salt incorporates a molecule of dimethylformamide.

Anal. Calcd for $C_{29}H_{31}BN_2O_5$: N, 5.62. Found: N, 5.51.

The salt may be obtained free of dimethylformamide as follows. A solution, prepared by mixing solutions of 2,2′-dihydroxybiphenyl (18.6 g, 0.1 mol) in warm methanol (100 ml) and boric acid (3.1 g, 0.05 mol) in boiling methanol (60 ml), was cooled in an ice bath and treated with anhydrous dimethylamine (3.4 g, 0.076 mol). Hexane (100 ml) was added to complete precipitation and the mixture was cooled in the freezer. The yield was 18.2 g (85.6%), mp 260–262° after crystallization from methanol–ether. A sample for analysis was dried in vacuo at 80° for 2.5 hr.

Anal. Calcd for $C_{26}H_{24}BNO_4$: N, 3.29. Found: N, 3.07.

When the above analytical sample was crystallized from dimethylformamide a molecule of the amide was again incorporated in the salt.

Anal. Calcd for $C_{29}H_{31}BN_2O_5$: N, 5.62. Found: N, 5.18.

Oxidation Potentials. These were determined on a PAR 170 Electrochemistry unit. A single compartment cell containing a silver wire reference electrode and platinum wire working and auxiliary electrodes was used. *p*-Phenylenediamine, $E_p = -0.15$ V vs. Ag/Ag^+ (0.1 *M*) in dimethyl sulfoxide, was used to calibrate the reference electrode. The observed anodic waves were all irreversible, and cathodic currents were not observed even at sweep speeds of 500 V/sec.

Registry No.—Boric acid, 10043-35-3; dimethylamine, 124-40-3; di-2-propylamine, 108-18-9; tetramethylammonium hydroxide, 75-59-2; tetraethylammonium hydroxide, 77-98-5; benzyltrimethylammonium hydroxide, 100-85-6; *p*-nitrobenzyltrimethylammonium hydroxide, 53993-52-5; *p*-xylylene bis(triethylammonium hydroxide), 29059-91-4; catechol, 120-80-9; 2,3-naphthalenediol, 92-44-4; 2,2′-dihydroxybiphenyl, 1806-29-7; dimethylformamide, 68-12-2; dimethylammonium borodi(o,o′-biphenolate) salt with dimethylformamide, 53993-07-0.

References and Notes

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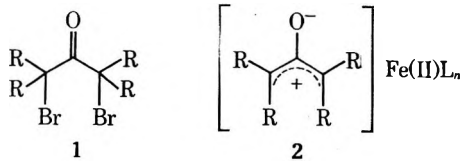
(3) G. Sivaramiah and V. R. Krishnan, *Indian J. Chem.*, **4**, 541 (1966); R. N. Adams, M. D. Hawley, and S. W. Feldberg, *J. Phys. Chem.*, **71**, 851 (1967).

A Method for the Generation of a Synthetic Equivalent of Unsubstituted Oxyallyl via the Bromo Ketone–Iron Carbonyl Reaction. A New Route to Thujaplicins[1]

Summary: Iron carbonyl promoted reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and cyclic 1,3-dienes followed by Zn–Cu couple reduction formally corresponds to a [3 + 4 → 7] cycloaddition of unsubstituted oxyallyl and dienes; synthesis of α- and β-thujaplicins using the cyclocoupling reaction as key step has been achieved.

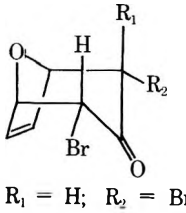
Sir: Reaction of α,α'-dibromo ketones **1** with $Fe_2(CO)_2$ generates the oxyallyl–Fe(II) species **2** (L = Br, CO, solvent,



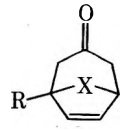
1 **2**

etc.) as reactive intermediate.[2] Its use in the synthesis of various cyclic systems has been demonstrated recently.[3] The limits were defined clearly by the type of the starting dibromides employable for the reaction. Secondary and tertiary dibromo ketones react with 1,3-dienes in a [3 + 4 → 7] manner to produce 4-cycloheptenones in good yields.[3a,d] However, attempted reactions with α,α'-dibromoacetone (**1**, R = H) were totally unsuccessful;[4] dibromides derived from other methyl ketones did not give satisfactory results either. Accordingly, for removal of this defect, thereby extending the use of the cyclocoupling reaction, discovery of suitable precursors which are synthetically equivalent to these methyl ketone dibromides would be required. This paper illustrates a simple two-step procedure surmounting this problem. The method consists of the generation of bromooxyallyls from polybromo ketones and removal of bromine atom(s) from the resulting cyclocoupling products.

For example, reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone (10 mmol) and $Fe_2(CO)_9$ (10 mmol) in dry furan (40 ml) (reflux, 38 hr) followed by the usual work-up gave a mixture of **3**, mp 119–120°, and **4**, mp 111–113°, in 57% combined



3, R_1 = H; R_2 = Br
4, R_1 = Br; R_2 = H



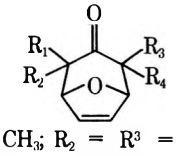
5, R = H; X = O
6, R = H; X = CH_2
12, R = $CH(CH_3)_2$; X = O

yield (after isolation, 9:1 ratio). These adducts were cleanly converted to the desired reduction product **5**, mp 37–39°, by exposure to 10 equiv of Zn–Cu couple[5] in methanol containing 5% of ammonium chloride (25°, 10 min) in >98% yield. Identity of **5** was established by comparison of the spectral data with reported ones.[6] The reaction of tetrabromoacetone (5 mmol) and excess cyclopentadiene with $Fe(CO)_5$ (6 mmol) in 1:5 tetrahydrofuran–benzene (80°, 45 min) followed by the Zn–Cu couple reduction led to the bicyclic ketone **6** in 60% yield.

Table I
Synthesis of 8-Oxabicyclo[3.2.1]oct-6-en-3-ones from Polybromo Ketones and Furan[a]

Starting bromide	Product[b]	Yield, %[c]
$\alpha,\alpha,\alpha',\alpha'$-Tetrabromoacetone	**5**	60[d]
1,1,3,3-Tetrabromobutan-2-one	**7**	63[e]
1,1,3-Tribromo-3-methylbutan-2-one	**8**	87
2,4-Dibromopentan-3-one	**9**	90[f-h]
2,4-Dibromo-4-methylpentan-3-one	**10**	84[f,i]
2,4-Dibromo-2,4-dimethylpentan-3-one	**11**	96[f,g]

[a] The reaction was carried out in furan using polybromo ketones (a mixture of diastereomers, when possible) and $Fe_2(CO)_9$ in a mole ratio of 1:1–1.2. [b] All new compounds gave correct analytical and spectral (ir, NMR, and mass) data. [c] Isolated yield. [d] The product is very volatile, and the yield was determined by NMR. [e] A single isomer having an equatorial methyl group. [f] Result of the single-step procedure. [g] See ref 3d. [h] A 1:1 mixture of equatorial–equatorial and equatorial–axial isomers. [i] A single isomer in which R_3 methyl is equatorial.

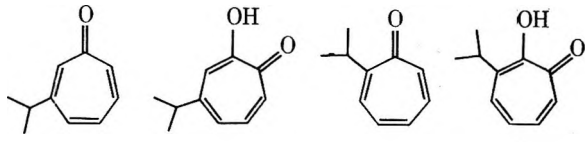


7, R_1 = CH_3; R_2 = R^3 = R_4 = H
8, R_1 = R_2 = CH_3; R_3 = R_4 = H
9, R_1 = R_3 = CH_3; R_2 = R_4 = H
10, R_1 = R_2 = R_3 = CH_3; R_4 = H
11, R_1 = R_2 = R_3 = R_4 = CH_3
15, R_1 = $CH(CH_3)_2$; R_2 = R_3 = R_4 = H

Since these products, **5** and **6**, are free from alkyl substituent at position α to carbonyl group, the two-step operation formally corresponds to a [3 + 4 → 7] cycloaddition involving an *unsubstituted* oxyallyl species as the three-carbon unit. 2-Methoxyallyl cation generated from 2-methoxyallyl halides and Ag(I) salts is known to cycloadd to these cyclic dienes, but only in lower yield.[6] Unsubstituted cyclopropanone, a molecule structurally related to oxyallyl, reacts with neither furan nor cyclopentadiene.[7]

The present modification possesses wide applicability. Tribromides of methyl ketones have also proved to serve as a simple and practical precursor of the reactive oxyallyl intermediates. Several examples of the reaction with furan are given in Table I. Thus, we are apparently in a position to be capable of generating 2-oxyallyls with no substitution as well as mono-, 1,1-di-, 1,3-di-, tri-, and tetraalkylation patterns, in a formal sense, via the bromo ketone–iron carbonyl reaction.[8]

With this versatile method now available, further application for the synthesis of troponoids should be stimulated. Firstly, the synthesis of β-thujaplicin (hinokitiol, **14**) has been accomplished by use of the bicyclic ketone **12** obtained from tetrabromoacetone and 2-isopropylfuran. Hydrogenation of **12** (10% Pd/C, C_2H_5OH, 96%), ether cleav-



13 14 16 17

age [$BF_3 \cdot OEt_2$–$(CH_3CO)_2O$, −10°, three products in 70%], bromination (1 equiv of NBS, 98%), and dehydrobromination (LiCl–DMF, 130°, 77%) gave the tropone **13**.[9] 3-Isopropylcyclohepta-2,6-dienone, one of the ether cleavage products, was also converted to **13** by treatment with DDQ–*p*-TsOH (benzene, 100°) in 80% yield. The tropone **13** was transformed to the tropolone **14** by the usual procedure ($NH_2NH_2 \cdot H_2O$ at 25° and then 2 *N* KOH at 80°, 100%).[10] The product was identical in all respects with the naturally occurring material.[11]

2-Isopropyltropone (**16**) has been prepared from **15** (derived from 1,1,3,3-tetrabromo-4-methylpentan-2-one and furan) by sequential treatments with H_2 over 10% Pd/C in C_2H_5OH (96%), BBr_3 in CH_2Cl_2 at −78–25° (giving 6-bromo-2-isopropylcyclohept-2-enone as major product in 70%), 1 equiv of Br_2 in CCl_4 (100%), and LiCl in DMF at 150° (20%). The tropone **16** can be converted to α-thujaplicin (**17**) by the known method.[12,13]

Acknowledgments. We thank Professors S. Itô and K. Takase and Drs. T. Toda and H. Fujise for a generous supply of natural thujaplicins. Partial financial support from the Takeda and Tokai Science Foundations is also acknowledged.

Supplementary Material Available. Illustrative experimental details will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-806.

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Received April 16, 1974

Direct Ring Fluorination of Aryl Oxygen Compounds with Xenon Difluoride

Summary: In the absence of hydrogen fluoride initiation, anisole, phenol, 2-naphthol, veratrole, catechol, and resorcinol react with xenon difluoride in methylene chloride or ether to give monofluoro substituted products in yields of 37–71%. Veratrole and catechol give the corresponding 4-fluoro compounds almost exclusively, while 2-naphthol is readily converted to 1-fluoro-2-naphthol.

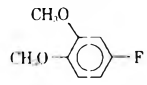
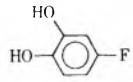
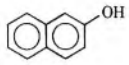
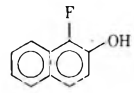
Sir: In the course of our studies on the synthesis of fluoro analogs of pharmacologically active compounds, we have examined the reaction of xenon difluoride with a variety of aryl oxygen compounds. The pioneering studies of Filler, Hyman, and Shaw[1–4] have demonstrated the utility of XeF_2 as a selective fluorinating reagent for aromatic hydrocarbons. In extending the scope of this reaction to include functionally substituted aryl compounds, we report here our results with methoxy- and hydroxy-substituted benzenes.

Xenon difluoride was prepared photochemically by a modification of Matheson's procedure.[5] The solvents dichloromethane and ether (Baker AR) were used without further purification. Anisole and veratrole were distilled before use, while phenol, catechol, resorcinol, and 2-naphthol were of reagent grade and used without further purification.

The procedure was adapted from that previously described.[1]

In a typical experiment, 4 g (37 mmol) of anisole (3-fold excess) dissolved in 12 ml of methylene chloride in a 30-cc Kel-F bottle was degassed to 5×10^{-6} Torr and poured onto 2.1 g (12.2 mmol) of xenon difluoride contained in an evacuated (5×10^{-6} Torr) Kel-F bottle at −196°. The resulting mixture was warmed gradually until the reaction commenced (as evidenced by the evolution of xenon gas and accompanying color change of the solution). Reactions usually occurred in the range of −10 to 25° and were complete within a matter of minutes for the monosubstituted benzenes and several hours for the disubstituted compounds. A small portion of the reaction mixture was treated with NaF pellets to remove the hydrogen fluoride produced and then analyzed by gas chromatography or mass spectrometry. For the remainder of the mixture, the solvent and HF were removed under reduced pressure (5–10 Torr) and the pure compounds were isolated by crystallization or fractional distillation. The results of these reactions are listed in Table I. In all cases, satisfactory yields (37–71%) of monofluorinated products were obtained. Mass spectral analysis failed to reveal any products due to fluorine addition. These reactions occur spontaneously upon warming to 25°. This behavior is in contrast to the reaction of XeF_2 and benzene which requires initiation by hydrogen fluoride. Presumably, the function of the HF is to polarize the Xe–F bond.[3] It is possible that this polarization can

Table I
Reactions of Oxygen-Substituted Benzenes with XeF_2

Substrate	Solvent	Fluorinated products[a]	% yield	Isomer distribn
$C_6H_5OCH_3$	CH_2Cl_2	$C_6H_4(OCH_3)F$	71.5	10:1:8[b]
C_6H_5OH	CH_2Cl_2	$C_6H_4(OH)F$	47	2:2:1[b]
$1,2\text{-}C_6H_4(OCH_3)_2$	CH_2Cl_2		37	
$1,2\text{-}C_6H_4(OH)_2$	$(C_2H_5)_2O$		38	
$1,3\text{-}C_6H_4(OH)_2$	$(C_2H_5)_2O$	$C_6H_3(OH)_2F$	45	Structure not yet established
	$(C_2H_5)_2O$		40	

[a] Column specifications for GLC separation of products: from anisole, 11 ft × ⅛ in., 2.5% Carbowax 20M on Chrom G (80–100 mesh); from phenol, 12 ft × ⅛ in., 10% Apiezon L on Chrom G (100–120 mesh); from veratrole, 6 ft × ⅛ in., 2.5% Carbowax 20M on Chrom G (80–100 mesh), non-acid-washed. The products from catechol, resorcinol, and 2-naphthol were solids which were purified by crystallization. The components of the mixtures of isomers of $C_6H_4(OCH_3)F$ and $C_6H_4(OH)F$ were identified and the yields were determined by comparison with authentic samples, using GLC. The fluoroveratrole, catechol, and 2-naphthol were isolated and compared with authentic samples. [b] Ortho:meta:para.

also be induced by dissolution of XeF_2 in a relatively polar solvent such as dichloromethane, perhaps via halogen–halogen interactions.

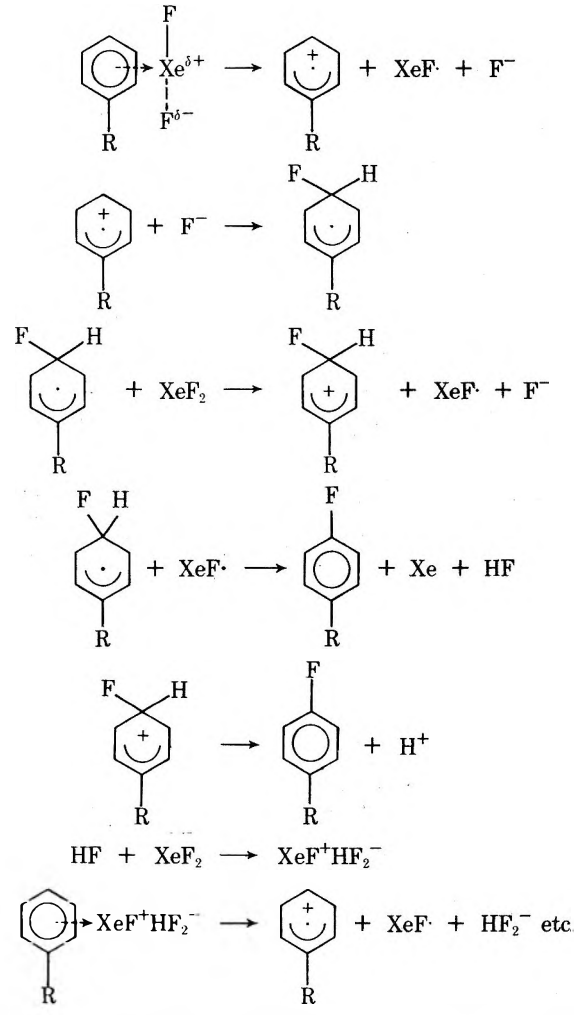
Since these reactions proceed without HF initiation, a modification of our previously proposed mechanism[3] is necessary. We tentatively suggest that substituted aromatic compounds, whose oxidation potentials are higher than that of benzene, induce the polarization of XeF_2 while transferring an electron, to form the colored cation radical (Scheme I). During the subsequent formation of fluorinated product, via a σ complex, hydrogen fluoride is generated and, as in the case of HF initiation, the rate of reaction is then markedly enhanced by the facile formation of the strongly oxidizing XeF^+. All of the compounds in this study possess oxidation potentials substantially higher than that of benzene.[6]

In the case of the phenols, the relatively high acidity ($pK_a \approx 9$–11)[7] does not appear to have any significant effect on the yield of fluorinated products. Apparently, the hydrolysis of XeF_2 by these phenols is much slower than nuclear fluorination. This is not surprising in view of the relatively slow aqueous hydrolysis of XeF_2 ($K_{15°} = 1.27 \times 10^{-4}$ sec^{-1}),[8] which is also unaffected by the presence of acid. Although the aqueous hydrolysis of XeF_2 yields the explosive xenon trioxide,[9] the reaction with phenols did not reveal any products containing a xenon–oxygen bond.[10] Moreover, there was no evidence of the oxidation of the phenols, as was observed with pentafluorophenol, to yield $(C_6F_5)_2O_2$.[11]

Anisole is converted to the isomeric fluoroanisoles (10:1:8 ortho:meta:para) while the fluorophenols are obtained in a markedly different ratio (2:2:1 ortho:meta:para). With both veratrole and catechol, the products are almost exclusively the 4-fluoro isomers. This orientation is consistent with the previously observed behavior of catechol[12] and veratrole[13] with electrophiles. Resorcinol is converted to a monofluoro product whose structure has yet to be confirmed. 2-Naphthol gives 40% 1-fluoro-2-naphthol (1) as the exclusive fluorine-containing product. In contrast, CF_3OF and 2-naphthol give 14% 1 and 20% 1,1-difluoro-2-naphthone.[14]

These results amply demonstrate the usefulness of XeF_2 as a selective, direct fluorinating agent for aryl oxygen compounds, thereby obviating multistep routes to the desired products. The yields have not been optimized and the full potential of this method remains to be explored.

Scheme I
Fluorination of Aromatics In the Absence of HF Initiation



Acknowledgments. We wish to thank Miss Nina Shoshoo for synthesizing some of the reference fluoro com-

pounds; Dr. M. Studier for his help with mass spectra; Dr. L. Kaplan, Dr. K. Wilzback, and Dr. W. Brown for their assistance with the gas chromatography work. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Supplementary Material Available. Description of a modified procedure for the preparation of XeF_2 and details for the reaction of the latter with anisole will appear following those pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-807.

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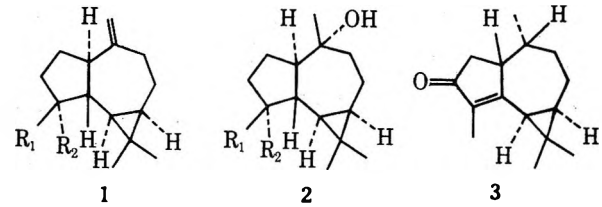
Received November 5, 1974

Photochemical Rearrangements of Cross-Conjugated Cyclohexadienones. Application to the Synthesis of (−)-4-Epiglobulol and (+)-4-Epiaromadendrene[1]

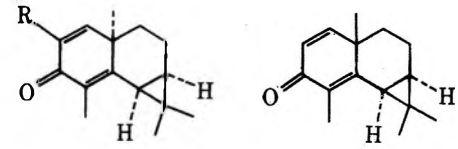
Summary: Photochemical rearrangement of (−)-dehydroepimaalienone (**5**) in aqueous acetic acid produced the tricyclic hydroazulene derivative **8** which was converted into (−)-4-epiglobulol (**2b**) and (+)-4-epiaromadendrene (**1b**).

Sir: In recent years there has been considerable interest in the synthesis of tricyclic sequiterpenes having a cyclopropane ring fused to a hydroazulene ring system, and syntheses of (−)-aromadendrene (the enantiomer of **1a**),[2] (±)-globulol (**2a**),[3] and (−)-cyclocolorenone (**3**)[4] have been reported. In our synthesis of (−)-cyclocolorenone the key step involved photochemical rearrangement of the carboxy cross-conjugated dienone **4b** to establish the ring skeleton of the natural product. We now wish to report the synthesis of (−)-4-epiglobulol (**2b**) and (+)-4-epiaromadrendene (**1b**)

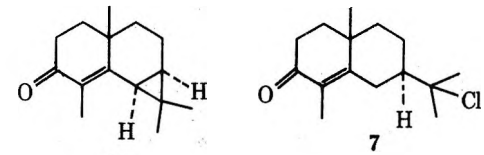


1 **2** **3**

a, $R_1 = H$; $R_2 = CH_3$
b, $R_1 = CH_3$; $R_2 = H$



4a, R = H
b, R = CO_2H **5**

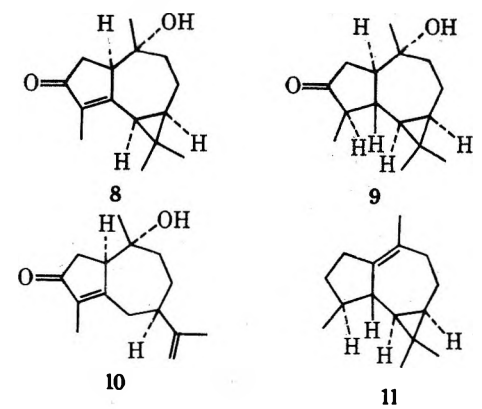


6 **7**

using photochemical rearrangement of the tricyclic dienone **5** to obtain the 5/7-fused system of these compounds.

A logical precursor to **5** was (−)-epimaalienone (**6**). While this compound has been prepared in six steps from α-santonin by Ourisson and coworkers,[5] a much more convenient route involved treatment of the bicyclic chloroenone **7**, an intermediate in our recently reported synthesis of (+)-α-cyperone,[6] with sodium hydride in 1,2-dimethoxyethane. Under these conditions ring closure via the conjugate enolate of **7** occurred to give **6** in 75% yield. Oxidation of **6** with 2,3-dichloro-5,6-dicyanobenzoquinone in dioxane gave **5** (56%): bp 111–115° (0.05 mm); λ_{max} (95% EtOH) 244 nm (ε 10,400) and 305 (8400); ir ν_{max} (CCl_4) 1654 (conjd C=O), 1622 (conjd C=C), 1585 cm^{-1} (conjd C=C); NMR $\delta_{(CH_3)_4Si}$ (CCl_4) 1.14 (s, 6 H), 1.24 (s, 3 H), 1.84 (s, 3 H), 6.08 (d, J_{AB} = 10 Hz, 1 H), 6.78 ppm (d, J_{AB} = 10 Hz, 1 H); *m/e* (70 eV) 216.153 (calcd 216.151); $[\alpha]^{25}D$ −367° (c 0.132, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.02; H, 9.39.

In contrast to its 10 epimer, **4a**, which has been shown to be stable to direct irradiation under a variety of conditions,[4,7] **5** was found to be photochemically labile.[8] Thus, on irradiation of a solution this dienone in 45% aqueous acetic acid at room temperature for 30 min using a 450-W Hanovia high-pressure mercury lamp housed in a Pyrex probe and chromatography of the photolysis mixture on silica gel, the tricyclic hydroxy ketone **8** was isolated in 50% yield. Compound **8** showed mp 93–95°; λ_{max} (95% EtOH) 251 nm (ε 11,300); ir ν_{max} (CCl_4) 3420 (OH), 1700 (conjd cy-



8 **9**

10 **11**

clopentenone), 1628 cm^{-1} (conjd C=C); NMR $\delta_{(CH_3)_4Si}$ (CCl_4) 0.80 (s, 3 H), 0.92 (s, 3 H), 1.18 (s, 3 H), 1.68 (d of d, J = 2 Hz, 3 H), 4.90 ppm (br absorption, 1 H); *m/e* (70 eV) 234.162 (calcd 234.162); $[\alpha]^{25}D$ −152° (c 0.111, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.64; H, 9.48. The uv absorption maximum at 251 nm indicated that the 1 hydrogen and the cyclopropane ring had the trans relationship in the photoproduct.[9] The cis relationship of the 1 hydrogen and the 10-hydroxyl group was assigned by analogy with the stereochemical results for related cases, e.g., the α-santonin–isophotosantonic lactone type rearrangements.[7b,10] Subsequent transformations provided support for this assignment.

Our original objective was to convert **8** into (−)-globulol (**2a**) by introduction of the appropriate stereochemistry at positions 4 and 5 by reduction and conversion of the carbonyl group to a methylene group. While this objective has not been realized as yet, we have been able to prepare (−)-4-epiglobulol (**2b**) in good yield. On treatment of **8** with 2.2 equiv of lithium in liquid ammonia and addition of ammonium chloride a single dihydro ketone having the structure **9** was produced in ~97% yield. Hydroxy ketone **9** had the following spectral properties: mp 68–69°; ir ν_{max} (CCl_4) 3600 (free OH), 3420 (hydrogen-bonded OH), 1740 cm^{-1} (cyclopentanone); NMR $\delta_{(CH_3)_4Si}$ ($CDCl_3$) 0.99 (s, 3 H), 1.06 (d, J = 6.5 Hz, 3 H), 1.09 (s, 3 H), 1.12 (s, 3 H); *m/e* (70 eV) 236.175 (calcd 236.178); $[\alpha]^{25}D$ −86° (c 0.072, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.11; H, 10.27. Compound **9** was unchanged on treatment with base which indicated that the more thermodynamically stable 4 epimer had been produced. Piers and Cheng[10f] have reported that on lithium–ammonia reduction the tricyclic hydroazulene **10** related to **8** gave a dihydro product having a trans ring fusion and a 4β-methyl substituent. They pointed out that, when the ring fusion is trans, the 4α-methyl group would be a destabilized by an eclipsed interaction with C-6. While this type of interaction would also exist in the 4α epimer of **9**, examination of models suggested that the 4β-methyl substituent might be destabilized to some extent by a steric interaction with the *endo*-methyl group on the cyclopropane ring. Thus it was hoped that a mixture of 4 epimers would be present at equilibrium. However, this was not the case, and no evidence for the presence of any of the 4α epimer of **9** was obtained.

Wolff–Kishner reduction of **9** afforded a single product which after chromatography on silica gel was isolated in 55% yield. This material showed mp 49–50°; ir ν_{max} (CCl_4) 3600 cm^{-1} (OH); NMR $\delta_{(CH_3)_4Si}$ ($CDCl_3$) 0.94 (d, J = 5.9 Hz, 3 H), 0.96 (s, 3 H), 1.02 (s, 3 H), 1.09 ppm (s, 3 H); *m/e* (70 eV) 222.196 (calcd 222.198); $[\alpha]^{25}D$ −16° (c 0.115, $CHCl_3$). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.04; H, 11.79. The spectral properties of this alcohol were very similar to but not identical with those of natural (−)-globulol[11] and the compounds had slightly different GLC retention times on a 6 ft × ⅛ in. 10% Carbowax K-20M on Chromosorb W column.

These results indicated that the Wolff–Kishner reduction product was 4-epiglobulol, i.e., **2b**. This was confirmed by reaction of the alcohol with thionyl chloride in pyridine at 0° followed by treatment with sodium acetate in acetic acid (to dehydrohalogenate the 10-chloro compound which was partially formed as an intermediate in the reaction). A 55% yield of a 4:1 mixture of two olefins was obtained. The major component was collected by preparative GLC using a 10 ft × ¼ in. 20% SE-30 on Chromosorb W column and exhibited identical spectral properties (ir and NMR) with those of (−)-4-epiaromadendrene.[2,12] Thus it had the structure **1b**. This olefin showed a specific rotation ($[\alpha]^{25}D$ +33° (c 0.050, $CHCl_3$) of nearly the same magnitude but of opposite sign to that reported ($[\alpha]^{25}D$ −31.4° (*c* 0.881, $CHCl_3$)) for its enantiomer.[2] The minor product obtained from dehydration of **2b** exhibited spectral properties which corresponded to the endocyclic olefin structure **11**. The formation of the exocyclic olefin as the major dehydration product of **2b** confirmed the assignment of the cis relationship between the 1-hydrogen atom and the 10-hydroxy group in the photoproduct **8**.[13]

The above results show that cyclohexadienone photolysis provides an excellent method of preparing tricyclic hydroazulenes containing a cyclopropane ring. Possible routes to allow the conversion of **8** into natural (−)-globulol (**2a**) are being explored.

Supplementary Material Available. Procedures for the preparation of new compounds reported in this paper will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th Street, N.W. Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-809.

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(11) We are grateful to Professors F. Šorm and P. R. Jefferies for providing us with authentic samples of (−)-globulol.
(12) We are grateful to Professor G. Büchi for providing us with copies of spectra of (−)-aromadendrene and (−)-4-epiaromadendrene.
(13) See paragraph regarding the availability of supplementary material for this paper.

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Highly Fluorinated Acetylenes. Preparation and Some Cyclization Reactions

Summary: Simplified preparations of new highly fluorinated acetylenes are described and a representative model undergoes thermal cycloaddition reactions to afford a cyclohexadiene, triazole, and cyclobutene.

Sir: Highly fluorinated acetylenes have been prepared previously by multistep synthetic routes[1] that invariably in-

volve a high-pressure reaction. A recent report,[2] disclosing the formation of a highly fluorinated acetylene from the copper initiated coupling between a perfluoro (F^3) primary alkyl iodide and an iodoacetylene, prompts this communication. We have found that fluorinated acetylenes also can be prepared from commercially available materials in ordinary apparatus by the following sequence of reactions.

$$R_fI + PhCH{=}CHBr \xrightarrow{i^a} R_fCH{=}CHPh \xrightarrow[2.\ iii]{1.\ ii} R_fC{\equiv}CPh$$

70–95% 60–90%

$$R_fI + ICH{=}CHCl \xrightarrow{i} R_fCH{=}CHCl \xrightarrow{iii} R_fC{\equiv}CH$$

50–70%

R_f = F-alkyl or alkylene ether

[a] i, DMF or DMAC, Cu (bronze), 100–120°, 16 hr; ii, Br_2, Freon 113, 25°, ~1–4 hr; iii, powdered KOH, distillation.

Several new fluorinated acetylenes prepared by these reactions which include, to the best of our knowledge, the first highly fluorinated diacetylene, are shown in Table I.

The reaction between F-alkyl iodides and halo olefins, the first step in our sequence, has been reported[4] for primary F-alkyl iodides; similar reactions using secondary F-alkyl[5] and F-vinyl[6] iodides also have appeared in the literature. We have observed that this reaction can be extended to certain F-alkylene ether iodides. Thus, structures such as $R_fOCF_2CF_2I$ give the expected product while $R_fOC(CF_3)FI$ structures afford only decomposition products involving scission at the C—O bond of the latter fluoro ether.

$$C_3F_7O(\overset{CF_3}{\underset{|}{C}}FCF_2O)_2\overset{CF_3}{\underset{|}{C}}FI + PhCH{=}CHBr \xrightarrow[DMF,\ 80^\circ]{Cu\ (bronze)} CF_3CF_2CH{=}CHPh$$

With regard to the above reaction it is suspected that the expected organocopper reagent forms and then decomposes to an F-ethylcopper species which subsequently reacts to give the observed product. This particular reaction is under further experimental scrutiny.

Once prepared, the highly fluorinated olefins can be converted to their corresponding acetylenes; however, in some cases complications arise. Compounds of the general structure $R_fCH{=}CHPh$ brominate and dehydrobrominate (KOH) smoothly to give the expected acetylene as the sole product. In contrast, the formation of $R_fC{\equiv}CH$ is accompanied by R_fH and other low boiling components. Since the $R_fCH{=}CHCl$ precursors studied were >95% trans, it is suspected that, on KOH treatment, trans loss of a positive chlorine (Cl^+) and negative R_f (R_f^-) leads to R_fH in competition with the acetylene-forming cis HCl loss.

Along these lines, it is noteworthy that the following reaction gives the internal acetylene only as a minor liquid product.

$$trans\text{-}C_7F_{15}CH{=}CHCF_3 \xrightarrow[2.\ KOH]{1.\ Cl_2} [C_7F_{15}CCl{=}CHCF_3 \text{ and/or } C_7F_{15}CH{=}CClCF_3] \xrightarrow{KOH}$$

$$C_7F_{15}H + C_7F_{15}C{\equiv}CH + C_7F_{15}C{\equiv}CCF_3$$

(4.5:4:1 relative ratio)

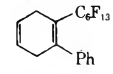
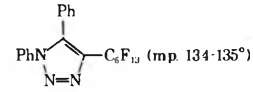
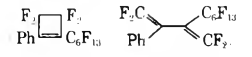
Our interest in highly fluorinated acetylenes stems from a possible polymer-forming reaction[7] between a diacetylene and various diunsaturates. Model reactions now have demonstrated that a representative highly fluorinated acetylene undergoes thermal [2 + 4], [2 + 3], and [2 + 2] cyclizations. Table II lists several new adducts from the interaction of F-hexyl-2-phenylacetylene and various unsaturated compounds indicative of the scope of these reaction systems.

Table I
Fluorinated Acetylenes

Acetylene[a]	Bp, °C (mm)	Yield from fluoro olefin, %
$C_8F_{17}C{\equiv}CH$	132–134	71
$C_6F_{13}C{\equiv}CPh$	58–61 (0.2) (bp[b] 227)	84
$(CF_2)_6(C{\equiv}CPh)_2$	160 (0.1)	60
$(CF_3)_2CFOCF_2CF_2C{\equiv}CPh$	68–71 (18)	65
$CF_3CF_2C{\equiv}CPh$	84–87 (50)	92

[a] The acetylenes have been characterized by infrared ($R_fC{\equiv}CH$: CH, 3.0 μ, C≡C, 4.65 μ; $R_fC{\equiv}CPh$: C≡C, 4.45 μ), ^1H and ^{19}F NMR, and either mass spectroscopy or elemental analysis. [b] Reference 2.

Table II
Products[a] from $C_6F_{13}C{\equiv}CPh$ Cycloadditions

Reactant	Products	Yield, %
$CH_2{=}CHCH{=}CH_2$		75
PhN_3	 (mp 134-135°)	76
$CF_2{=}CF_2$	 (19:2 relative ratio)	70

[a] The acetylene adducts have been characterized by ^1H and ^{19}F NMR, infrared, and either mass spectroscopy or elemental analysis.

The above reactions are clean; unreacted starting material accounts for the material balance (>98%).

Acknowledgment. We gratefully acknowledge National Aeronautics and Space Administration support under Contract NAS2-8156. Thanks are due to Dr. E. C. Stump, Jr., for his interest in this work and Mr. B. W. Cameron for his capable technical assistance.

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Received December 16, 1974

Copper(I)-Promoted Thiophenoxide Ionization in Solution. A Simple Synthesis of Vinyl Phenyl Sulfides

Summary: The concept of carbonium ion generation by the action of cuprous ion on thioacetals and thioketals is applied to the preparation of vinyl sulfides and a furan.

Sir: A common method of initiating carbonium ion reactions in nonprotic solvents is the removal of a halide ion from a suitable alkyl halide by a soluble Lewis acid such as an antimony pentahalide,[1] an aluminum trihalide,[1] or silver nitrate.[2] A soluble Lewis acid for the removal of the thiophenoxide ion from alkyl thiophenoxides would have considerable potential use in such reactions because of the ready availability of compounds bearing the thiophenoxide group; this availability arises partly from the facile high-yield conversion of aldehydes and ketones into thioacetals and thioketals by the action of thiophenol and acid (eq 1)[3] and partly from the ability of the thiophenoxide group to stabilize a negative charge thus permitting the construction of a compound containing the SPh group from precursors containing fewer carbon atoms (e.g., eq 2).[4]

$$RCOR' + 2C_6H_5SH \xrightarrow{H^+} RC(SPh)_2R' + H_2O \quad (1)$$

$$(PhS)_2C(R)Li + R'X \longrightarrow (PhS)_2C(R)R' + LiX \quad (2)$$

We now report that cuprous ion, supplied as the benzene complex of cuprous trifluoromethanesulfonate[5] (triflate), a substance which is soluble in a number of organic solvents, is a strong Lewis acid toward thiophenoxide. One application of this finding is a simple, general, high-yield synthesis of vinyl phenyl sulfides (1) by the elimination of thiophenol from thioacetals and thioketals (1.9 mmol) induced by the benzene complex of copper(I) triflate (3.8 mmol, containing 7.6 mg-atoms of Cu^+) in benzene (30 ml)/THF (10 ml) under N_2 (eq 3). For most simple substances (prepared by eq 1 or 2), the reaction occurs at room temperature (Table I).[6] In most cases by-products are not formed and the product is readily isolated by adding water, filtering, and extracting with ether. Insoluble cuprous iodide is ineffective. Previously reported procedures for effecting such an elimination involve pyrolysis in the presence of strong acid[3a,7] or conversion to the sulfoxide and pyrolytic elimination of benzenesulfenic acid.[8] The strong acidity, which develops during the reaction, can be avoided in the case of acid-sensitive products by the presence of 2,6-lutidine or diisopropylethylamine which are readily removable from the product by acid extraction or silica chromatography. An attractive feature of this procedure is its apparently irreversible nature; in most cases the cuprous thiophenoxide precipitates from solution. Two closely related applications are the syntheses of (1) 1-thiophenoxy-1,3-butadiene (**2**,[9] two geometric isomers) by performing the elimination (46°, 24 hr) on the product of the reaction of the lithium salt of dithiophenoxymethane[4] with allyl bromide and (2) ketene diphenyl thioacetal (**3**)[10] by elimination (25°, 5 min) from the

$CH_2{=}CHCH{=}CHSPh$ (**2**) $\qquad CH_2{=}C(SPh)_2$ (**3**)

product of methylation of the lithium salt of trithiophenoxymethane,[11] both in the presence of lutidine.[12]

Vinyl sulfides and ketene dithioacetals are valuable reactants in a number of synthetic procedures.[9,13] No single method previously available[13a,14-16] would be applicable to the preparation of all of the vinyl sulfides reported here and, in many individual cases, this appears to be the preferred procedure because of its high yield and simplicity.

The reactivity order (Table I) is clearly that expected for rate-determining cation formation.[17] This is also indicated by the smooth production of 2-phenyl-5-methylfuran (**6**) from the adduct (**5**) of methyl vinyl ketone and the cuprate (**4**)[18] derived from the thioacetal of benzaldehyde (eq 4); in this case, the cation is apparently trapped by the carbonyl group before undergoing proton loss.

$$[PhC(SPh)_2]_2CuLi \xrightarrow{MVK} \underset{\mathbf{4}}{} \qquad PhC(SPh)_2CH_2CH_2\overset{O}{\overset{\|}{C}}Me \xrightarrow[<5\text{ min }80\%]{Cu^+,\ 25^\circ} \underset{\mathbf{6}}{\text{2-Me, 5-Ph furan}} \quad (4)$$

$\mathbf{5}$

Another application is the alkylidenation of a suitable alkyl halide (eq 5).[19] The utility of such a sequence for the general synthesis of conjugated olefins is being explored as well as the generality of the furan synthesis and a number of other synthetic uses of this cation-forming reaction.

$$PhCH_2Br + PhCH(Li)SPh \longrightarrow$$

$$PhCH(CH_2Ph)SPh \xrightarrow[>95\%]{Cu^+,\ 39\text{ hr},\ 58^\circ} PhCH{=}CHPh\ (\sim 99\%\ \text{trans}) \quad (5)$$

Table I
Elimination of Thiophenol from Thioacetals and Thioketals Induced by Cuprous Triflate in Benzene–THF at 25°[a]

$$R(R')CHC(SPh)_2R'' + C^+ \xrightarrow[THF]{C_6H_6} RR'C{=}C(SPh)_2R'' + CuSPh + H^+ \quad (3)$$

R	R′	R″	Time[b]	Cu^+/substrate	% yield[c]
Me	H	H	3 hr	4	91[d]
Ph	H	H	8 hr	6.1	90[e]
Ph	H	H	72 hr	1.2	93[f]
Me	Me	H	1.5 hr	3	85
H	H	Ph	<5 min	2[g]	85[h]
H	$-CH_2CH_2CH_2CH_2-$		10 min	2	92
$-CH_2CH_2CH_2CH_2CH_2-$		H	1 hr	2	92
Me	Me	Me	<5 min	2.4	94[i]

[a] Syntheses were conducted on ca. a 2-mmol scale except for the last entry in which 10.4 mmol of thioketal was employed. [b] For disappearance of substrate (TLC). [c] Isolated yields. [d] Over 90% trans by GLC; when the synthesis was performed at reflux (1 hr), the product was all trans. [e] One half trans. [f] Two thirds trans. [g] Diisopropylethylamine present. [h] Product was contaminated with 6% acetophenone. [i] Product was 2-thiophenoxy-3-methyl-2-butene as indicated by refractive index, TLC, GLC, and NMR; no trace of the positional isomer could be detected.

Acknowledgment. This work was supported by the National Institutes of Health, the Health Research and Services Foundation, and Science Development Grant GU-3148 from the National Science Foundation.

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Received December 24, 1974

A Remarkable Rearrangement and Elimination Reaction in the Solvolysis of Tertiary α-Chloroboronates under Mild Conditions

Summary: Tertiary α-chloroboronic esters, readily available from the base-induced reaction of borinic esters with dichloromethyl methyl ether, undergo a remarkable rearrangement (with hydride or methide shifts) and elimination during solvolysis in aqueous solvents to produce the corresponding olefins in high yield.

Sir: Solvolysis of tertiary α-chloroboronates in 50% aqueous ethanol proceeds via hydride or methide shifts with the concurrent loss of the elements of chlorodimethoxyborane to form the corresponding olefin (eq 1). The reaction occurs essentially instantaneously at room temperature in the presence of aqueous silver nitrate, providing an exceptionally mild route to internal olefins in high yield (eq 2).

Table I
Products Obtained in the Alkaline Hydrogen Peroxide Oxidation of α-Chloroboronic Esters, $RR'CClB(OCH_3)_2$

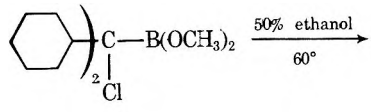
R	R′	Ketone,[a] %	Olefin,[a,c] %
Isobutyl	Isobutyl	86[b] (56)[c]	~10
Cyclopentyl	Cyclopentyl	86[b] (59)[c]	~10
exo-Norbornyl	*exo*-Norbornyl	62	29
Cyclohexyl	Cyclohexyl	95	0
3-Methyl-2-butyl	3-Methyl-2-butyl	54[b]	30
2,3-Dimethyl-2-butyl	Cyclopentyl	43[d]	35
2,3-Dimethyl-2-butyl	Cyclohexyl	31[d]	29

[a] By GLC on a 6 ft × 0.25 in. 10% SE-30. [b] 1 equiv of DCME and 2 equiv of base were used. [c] 1 equiv of DCME and 1 equiv of base were used. [d] 2 equiv of DCME and 2 equiv of base were used.

Table II
Olefin Formation by the Reaction of α-Chloroboronic Esters, $RR'CClB(OCH_3)_2$, with Silver Nitrate in 50% Ethanol at 25°

R	R′	Olefin[a]	Yield,[b] %
Cyclohexyl	Cyclohexyl	Cyclohexylidenecyclohexane	83
exo-Norbornyl	*exo*-Norbornyl	2-Norbornylidene-*exo*-norbornane	81
2,3-Dimethyl-2-butyl	Cyclopentyl	2-Cyclopentyl-3,4-dimethyl-2-pentene[c]	82

[a] By GLC on a 10% SE-30 column. [b] No other organic products were detected. [c] The stereochemistry of the methyl groups was not determined.



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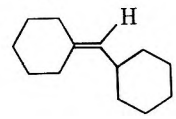
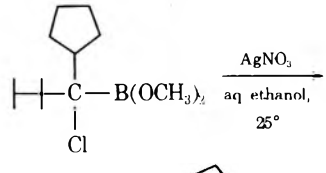
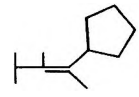


+ HCl + $2CH_3OH$ + $B(OH)_3$ (1)

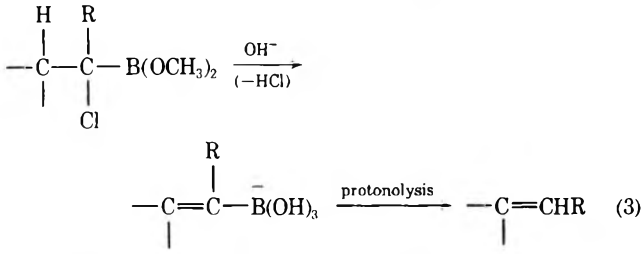




+ AgCl + $B(OH)_3$ + $2CH_3OH$ (2)

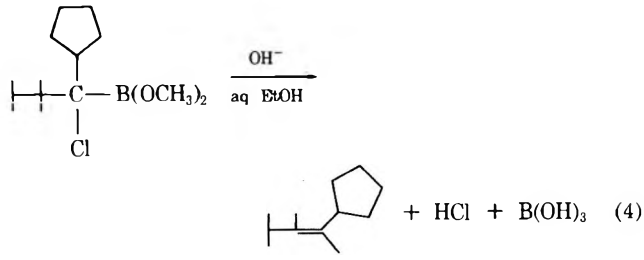
In the course of the alkaline hydrogen peroxide oxidation of α-chloroboronic esters to ketones,[1] we observed formation of internal olefins in significant amounts accompanying the formation of the desired ketones. The amount of the olefin increased for the more hindered cases (Table I). In exploring the factors responsible for olefin formation, the reaction was carried out omitting hydrogen peroxide.

However, the same olefins were produced. The possibility was next considered that the reaction might proceed through an E2 elimination of hydrogen chloride, followed by protonolysis of the resulting vinylboronate (eq 3). This



(3)

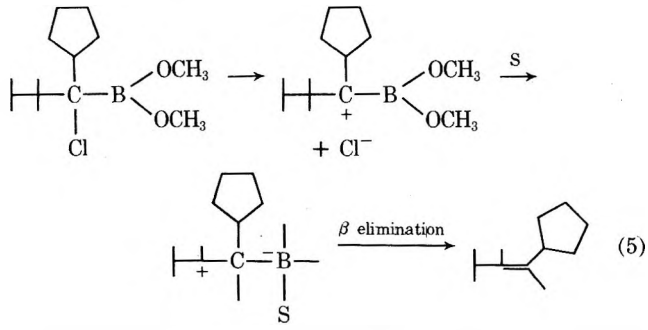
possibility was excluded on the basis of the following observations. (1) The methyl migration obtained in the thexylcyclopentyl case would be difficult to rationalize in terms of a vinylboronate intermediate (eq 4). (2) Protonolysis of



(4)

vinylboronates is a very slow process under alkaline conditions.[2] (3) No deuterium is incorporated into the olefinic side products in the oxidation of the reaction products from both methyl bis(*trans*-2-methylcyclopentyl)borinate and methyl thexylcyclopentylborinate with DCME and base in deuterium oxide. Finally, (4) hydrolysis of 1 in 50% aqueous ethanol at 60° in the absence of base also yields the olefin (eq 1).

A possible explanation for these results is a mechanism involving the ionization of the chlorine substituent to produce the corresponding carbonium ion which then undergoes fast hydride (or methide) migration, followed by β elimination (eq 5).



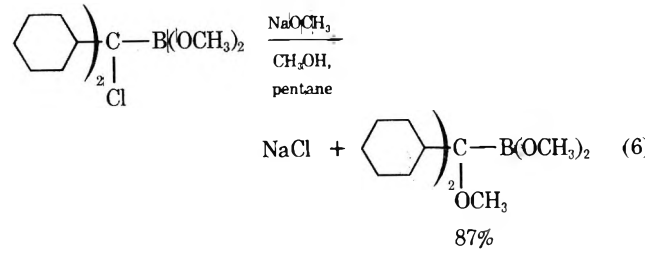
(5)

This mechanism is also compatible with the facile vapor phase decomposition of these tertiary α-chloroboronates.[3]

If this carbonium ion mechanism is indeed the pathway, it appeared possible that the reaction could be facilitated by aqueous silver nitrate. Indeed, addition of a molar equivalent of silver nitrate to a solution of α-chloroboronate in ethanol leads to instantaneous precipitation of silver chloride. Analysis of the reaction mixture by NMR and gas chromatography reveals the presence of olefins in yields above 80%/ The results are summarized in Table II.

A representative procedure follows. To 5.0 mmol of the α-chloroboronate dissolved at room temperature in 5 ml of absolute ethanol under nitrogen is added 5.5 mmol of silver nitrate in 5 ml of distilled water. An immediate precipitate forms. The mixture is stirred an additional hour at 25°. The mixture (after addition of 5 ml of pentane) can be analyzed by GLC, using a hydrocarbon as internal standard. Alternatively, the olefin can be isolated by first filtering the silver chloride and then washing the precipitate with 2 × 10 ml of water and 2 × 10 ml of pentane. Distillation of the dried organic layer yields the olefin. The physical properties of the olefins, as well as their structures, are similar to those reported in the pyrolysis of α-chloroboronic esters.[3]

The elimination reaction could be avoided and substitution[4] of the chloride atom successfully accomplished by treating a 1.0 *M* solution of α-chloroboronate in pentane with 1 equiv of sodium methoxide in anhydrous methanol (eq 6). The product, dimethyl (dicyclohexylmethoxycarbinyl)boronate, mp 68–70°, is obtained in 87% yield. NMR confirmed the product to be the α-methoxy derivative. A singlet at δ 3.28 (3 H) was observed for the *C*-methoxy protons and another singlet at δ 3.63 (6 H) for the *B*-methoxy protons. Such replacement of the chlorine atom by a methoxy group, prior to the oxidation by alkaline hydrogen peroxide, avoids significant formation of olefins as side products and markedly improves the yields of ketone over those reported in Table I. Thus, it is possible by variation in the reaction conditions to achieve a facile conversion of α-chloroboronic esters to olefins or to the α-methoxy derivatives, readily oxidized to ketones.



(6)

87%

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(5) Graduate research assistant on Grant GM 10937 supported by the National Institutes of Health.
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Received November 25, 1974

A General One-Carbon Homologation of Organoboranes via α-Thioorganoborate Anions

Summary: The reaction of trialkylboranes with thiomethoxymethyllithium or 2-lithiothiomethoxy-1,3-thiazoline, followed by the treatment of the resultant α-thioorganoborate complexes with methyl iodide, produces the one-carbon homologated organoboranes in high yields.

Sir: We wish to report a novel procedure for the one-carbon homologation of organoboranes via α-thiorganoborate anions.[1]

The reaction of tri-*n*-butylborane with the α-lithio derivatives of methyl phenyl sulfone,[2] dimethyl sulfoxide,[3] and dimethyl sulfide[4] produces the corresponding organoborate complexes **1**, **2**, and **3**, as judged by ^{1}H NMR[5] [(THF–hex-

Table I
One-Carbon Homologation of Organoboranes via the Reaction of α-Thioorganoborate Anions with Methyl Iodide[a]

Organoborane	Homologation reagent[b] (equiv)	Product after oxidation[c] (mmoles)
Tri-*n*-butyl-	A (1)	*n*-Pentanol (9.7), *n*-butanol (19.3)[d,e]
	B (1)	*n*-Pentanol (8.9), *n*-butanol (19.7)[d]
Tris-(2-methylpentyl)-	B (3)	2-Methylhexanol (9.2), 2-methylpentanol (20.8)
Tricyclopentyl-	B (1)	Cyclopentylmethanol (7.1), cyclopentanol (22.1)
	B (2)	Cyclopentylmethanol (8.2), cyclopentanol (20.5)
	B (3)	Cyclopentylmethanol (9.7), cyclopentanol (21.0)
Trinorbornyl-	A (3)[f]	2-Norbornylmethanol (8.3), 2-norbornanol (20.5)
	B (3)	2-Norbornylmethanol (6.6), 2-norbornanol (22.0)
Thexyldi-*n*-pentyl-[g]	A (2)[h]	*n*-Hexanol (8.8), *n*-pentanol (11.0), thexyl alcohol (9.7)[i]
Disiamyl-*n*-pentyl-[j]	A (1)	*n*-Hexanol (2.1), *n*-pentanol (7.2), 2,3-dimethyl-1-butanol (6.7), 2-methyl-2-butanol (12.9)
B-Phenyl-9-BBN[k]	A (3)[f]	Benzyl alcohol (7.3), phenol (1.8), 1,5-cyclooctanediol (8.3) 5-hydroxycyclooctylmethanol (1.1)
B-(*p*-Methoxyphenyl)-9-BBN[k]	A (2)[h]	*p*-Methoxybenzyl alcohol (8.4), *p*-methoxyphenol (1.1), 1,5-cyclooctanediol (8.0), 5-hydroxycyclooctylmethanol (1.2)
Disiamyl-*trans*-1-hexenyl-[j]	A (3)[f]	*trans*-2-Hepten-1-ol[l] (7.2), 1-hepten-3-ol (0.5), 2,3-dimethyl-1-butanol (2.9), 2-methyl-2-butanol (17.4)[m]

[a] In THF–hexane at ~25° after addition of methyl iodide at 0°. A threefold excess of methyl iodide was used unless otherwise stated. [b] A, thiomethoxymethyllithium–TMEDA; B, 2-lithiothiomethoxythiazoline. The numbers in parentheses are the amount of the reagent relative to that of the organoborane. [c] The amount of each product is based on 10 mmol of the organoborane used. [d] The amount of 1-butanol includes ~1.5 mmol of 2-butanol. Only a trace of 2-methyl-1-butanol was present. [e] The yield of di-*n*-butylmono-*n*-pentylborane containing minor amounts (~15%) of two other by-products was 93% by GLC (SE-30). [f] A ninefold excess of methyl iodide was used. [g] thexyl, 2,3-dimethyl-2-butyl. [h] A sixfold excess of methyl iodide was used. [i] Only a trace of 2,2,3-trimethyl-1-butanol was present. [j] siamyl, 3-methyl-2-butyl. [k] 9-BBN, 9-borabicyclo[3.3.1]nonane. [l] Only a trace of the cis isomer was present. [m] A few other minor unidentified products were present.

$Li[n\text{-}C_4H_9)_3BCH_2SO_2Ph]$ (1) $Li[n\text{-}C_4H_9)_3BCH_2SOCH_3]$ (2) $Li[n\text{-}C_4H_9)_3BCH_2SCH_3]$ (3)

ane, benzene) δ −0.45 to ca. +0.25 (6 H for α-methylene protons) ppm relative to $(CH_3)_4Si$] and ir[5,6] [(THF–hexane) ~2740 cm^{-1} for α-methylene C–H stretching]. Whereas treatment of **1** with alkylating agents, such as methyl fluorosulfonate, induces an *intermolecular* carbon–carbon bond formation producing ethyl phenyl sulfone, the corresponding reaction of **3** results in an *intramolecular* carbon–carbon bond formation producing di-*n*-butylmono-*n*-pentylborane[7] (**4**) in nearly quantitative yield (93%).[8] When a 1:1 mixture of tri-*n*-butylborane and tri-*n*-pentylborane was used, none of the cross-over products, such as di-*n*-butylmono-*n*-hexylborane, was detected by GLC, indicating the intramolecular nature of the carbon–carbon bond formation (eq 1).

$$R_3B^-CH_2SCH_3 \xrightarrow{CH_3I} \left[R_2\text{-}B(R)\text{-}CH_2\text{-}S^+(CH_3)_2 \right] \longrightarrow R_2BCH_2R + S(CH_3)_2 \quad (1)$$

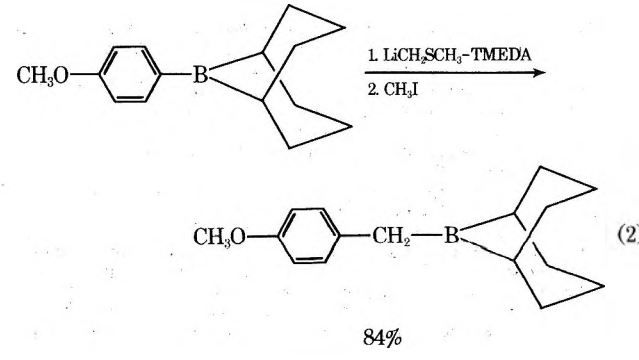
Although the reaction of organoboranes with certain ylides achieves a similar homologation,[9] there are major differences between the organoborane–ylide reaction and the organoborate–electrophile reaction. First, the latter is far less sensitive to the steric hindrance and is therefore of greater generality.[10] Second, the organoborane–ylide reaction can be complicated by the multihomologation. Such a multihomologation has not been observed in the latter even when excessive quantities of α-thioalkyllithiums and electrophiles were used. This makes possible to force the homologation reaction to go to completion.

The highest yields of homologated products have been observed with methyl iodide as an electrophile, although other reagents, such as methyl fluorosulfonate, benzyl chloride and benzoyl chloride, also give satisfactory results.

Although both thiomethoxymethyllithium–TMEDA[4] (**5**) and 2-lithiothiomethoxy-1,3-thiazoline[11] (**6**) are satisfactory as homologation reagents, the procedure using **5** appears to be less sensitive to the steric requirement of organoboranes. However, **6** can offer an advantage in that it can have an organic substituent on the methyl carbon atom.[12]

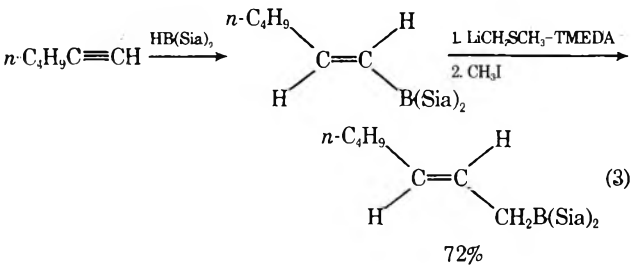
The homologation reaction reported here is general as indicated by the results summarized in Table I. It should be noted that the homologated organoboranes prepared in this study are not readily accessible by the simple hydroboration or transmetalation methods.

A few unique applications of the one-carbon homologation procedure are the conversion of arylboranes into the corresponding benzylboranes (eq 2) and that of alkenylboranes into the corresponding allylboranes (eq 3). The trans geometry of disiamyl-2-heptenylborane was established by spectral examinations [ir (neat) 970 cm^{-1} (s)] and the gas chromatographic comparison of 2-hepten-1-ol obtained after oxidation with its authentic sample. Since a variety of *trans*-alkenylboranes can be readily obtainable by the hydroboration of the corresponding acetylenes, the reaction offers, for the first time, a *stereoselective*[13] synthesis of stereochemically defined allylic organoboranes. We are cur-



(2)

84%



Sia = 3-methyl-2-butyl

rently exploring the scope and limitations of this highly promising synthesis as well as the possibility of applying the homologation procedure to the organoborane ring expansion.

The following procedure is representative. To a solution of 10 mmol of thiomethoxymethyllithium–TMEDA in hexane prepared by the literature procedure[4] and placed in a 100-ml flask equipped with a septum inlet, a magnetic stirring bar, and an outlet connected to a mercury bubbler was added 2.44 ml (10 mmol) of tri-*n*-butylborane in 10 ml of THF at 0°. After the mixture stirred for 1 hr at 0°, 1.87 ml (30 mmol) of methyl iodide was added at 0°, and the reaction mixture was stirred for 6 hr at 25°. After addition of *n*-hexadecane as an internal standard, the mixture was oxidized with 10 ml each of 3 *N* sodium hydroxide and 30% hydrogen peroxide. After the aqueous layer was saturated with potassium carbonate, GLC examination (Carbowax 20M) indicated the presence of *n*-pentanol (9.7 mmol), 1-butanol (17.8 mmol), 2-butanol (1.5 mmol), and a trace of 2-methyl-1-butanol. In a separate run, the reaction mixture was examined by GLC (SE-30) before oxidation. There was present di-*n*-butylmono-*n*-pentylborane (93%) accompanied by two minor by-products (~15% of the total products). This product was identified by GLC isolation followed by alkaline hydrogen peroxide oxidation which produced a mixture of the alcohols in a ratio almost identical with that reported above. Essentially no tri-*n*-butylborane remained unreacted.

Acknowledgment. We thank the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Syracuse University for support of this work.

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(6) These complexes are stable at 25° for at least several hours. On heating, they undergo slow decomposition reactions. The precise courses of such reactions have not been examined in detail.
(7) Tri-*n*-butylborane contains ~15% of di-*n*-butylmono-sec-butylborane and 1–2% of mono-*n*-butyldi-sec-butylborane. Although two minor products that accompanied di-n-butylmono-*n*-pentylborane have not been identified, the GLC pattern is nearly identical with the original three-peak pattern.
(8) The reaction of **2** with methyl fluorosulfonate produced **4** in 14% yield: unpublished results obtained with K. W. Chiu.
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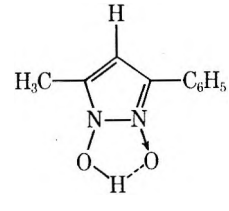
Received November 12, 1974

Isolation of a New 1-Hydroxypyrazole 2-Oxide via Chelation

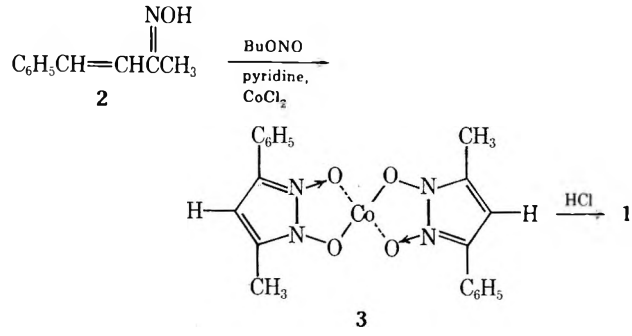
Summary: The isolation of 1-hydroxy-3(5)-phenyl-5(3)-methylpyrazole 2-oxide via a metal complex by nitrosation of benzalacetone oxime in the presence of cobaltous chloride is reported, and the intermediacy of this compound in the formation of 3,4-diazacyclopentadienone derivatives is demonstrated.

Sir: We wish to report the isolation of 1-hydroxy-3(5)-phenyl-5(3)-methylpyrazole 2-oxide (**1**). Although several 1-hydroxypyrazole 2-oxides have been prepared by Freeman and Gannon,[1] this is the first case in which the pyrazole ring is not fully substituted.



1

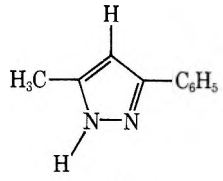
The procedure used in the isolation of **1** involved the preparation of a solution in aqueous ethanol of benzalacetone oxime (**2**), pyridine, and cobaltous chloride[2] in a molar ratio of 1:1:0.5. This solution was treated with 1.3 equiv of *n*-butyl nitrite which was added in three equal portions at 90-min intervals. The crude precipitate, chiefly the cobalt chelate (**3**),[3] was extracted with warm, concentrated HCl, and an insoluble by-product was filtered off.[4] Upon dilution of the filtrate with water and cooling, **1** was isolated in 33% yield.



The product was only sparingly soluble in most solvents, but with aqueous KOH it formed a stable salt which was readily purified by recrystallization from ether–tetrahydrofuran. A pure sample of **1** regenerated from the potassium salt was a white solid, melting with decomposition at 182°. (Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.31; N, 14.72.

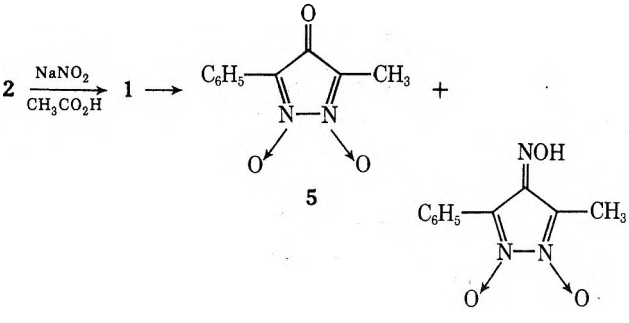
Found: C, 62.88; H, 5.35; N, 14.54.) The compound yellowed slowly upon exposure to air and light.

The chemical properties (acidity, chelation) and spectral characteristics of 1 agree with those of previously reported 1-hydroxypyrazole 2-oxides.[1b] The infrared spectrum closely resembled that of a sample of 1-hydroxypyrazole-3(5)-phenyl-4,5(3)-dimethylpyrazole 2-oxide, while the NMR spectrum (CF_3CO_2H) showed signals at δ 7.80–8.90 (m, 5, C_6H_5), 6.47 (s, 1, pyrazole C-4 proton), and 2.52 (s, 3, CH_3).[5] The heterocyclic structure was confirmed by reduction of 1 with zinc in refluxing acetic acid to 3(5)-phenyl-5(3)-methylpyrazole (4), identified by comparison with an authentic sample.[6]



4

Although 1 has not been isolated previously, its intermediacy has been inferred in the nitrosation of 2 with sodium nitrite in acetic acid to give 2-phenyl-5-methyl-3,4-diazacyclopentadienone 3,4-dioxide (5) and the corresponding oxime (6).[7] In a preliminary investigation of its chemical reactivity, 1 was subjected to nitrosation under conditions approximating those reported for the conversion of 2 to 5 and 6. When the nitrosation was performed under an inert



5 6

atmosphere, the main product was 6, while the ketone (5) was the major product when the reaction mixture was kept saturated with oxygen during the nitrosation. These results support the intermediacy of 1 in the synthesis of 5 and 6 as proposed by Freeman.

We are currently pursuing further investigations into the synthesis and reactivity of 1 and analogous compounds.

Acknowledgment. The authors are grateful to the Donors of the Petroleum Research Fund, administered by the Americal Chemical Society, for partial support of this research.

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(2) We believe, as proposed by Freeman,[7] that 1 is present during the nitrosation of **2**, even in the absence of the metal, but undergoes further reaction under nitrosating conditions. Cobalt(II), under basic conditions, simply traps the anion of 1 by forming a very insoluble chelate which is removed from the nitrosating medium before further reaction occurs. The formation of such chelates with 1-hydroxypyrazole 2-oxides has been reported for a variety of metal ions,[1b] and we are investigating the behavior of other metal ions in place of cobalt(II) in our reaction.
(3) The chelate (**3**) was isolated from the crude product mixture after extraction with methanol in a Soxhlet extractor for several hours. The insoluble residue recovered from the Soxhlet thimble was identical in the infrared with an analytical sample of **3**,[5] a violet solid, subsequently prepared by treatment of the potassium salt of 1 with aqueous $CoCl_2$.
(4) The by-product was identified as the oxime (**6**). In the absence of the metal ion, the reaction gave **6** in 42% yield, and no isolable quantities of 1 were detected.
(5) Spectra were obtained using a Beckman IR-8 infrared spectrophotometer and a Hitachi Perkin-Elmer R 20 60-MHz NMR spectrometer.
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Received September 17, 1974

Synthetic Organic Photochemistry. VII. Six-Atom Photochemical Ring Expansions[1]

Summary: The photolysis of 2-(2-cyclopropylcyclopropyl)cycloalkanones leads to a six-atom ring expansion in a single step.

Sir: Traditional methods for the ring expansion of carbocyclic systems most frequently involve one atom ring expansions.[2] We have been engaged for some time in a program aimed at developing methods by which rings can be expanded by several atoms in a single step. Previously we have reported examples of two atom photochemical ring expansions of 2-alkenyl-[3] and 2-alkynylcycloalkanones[4] and three atom photochemical ring expansions of 2-cyclopropyl-[5] and 2-oxiranylcycloalkanones.[6] In order to increase the utility of the photochemical method of ring expansion we have sought to prepare systems which combine two of the above types of structural features and herein report our initial studies in this area.

A 2-(2-cyclopropylcyclopropyl)-cycloalkanone such as **1** is an attractive model system because it can potentially undergo a six atom photochemical ring expansion either by a one photon (path a, Scheme I) or by a two photon process (path b).[7] The route illustrated in Scheme II, which makes use of a recently reported synthesis of α,β-unsaturated aldehydes using 1,3-bis(methylthio)-allyllithium,[8] provided an efficient method for the preparation of **1a** and **1b** from the corresponding cycloalkene oxides.

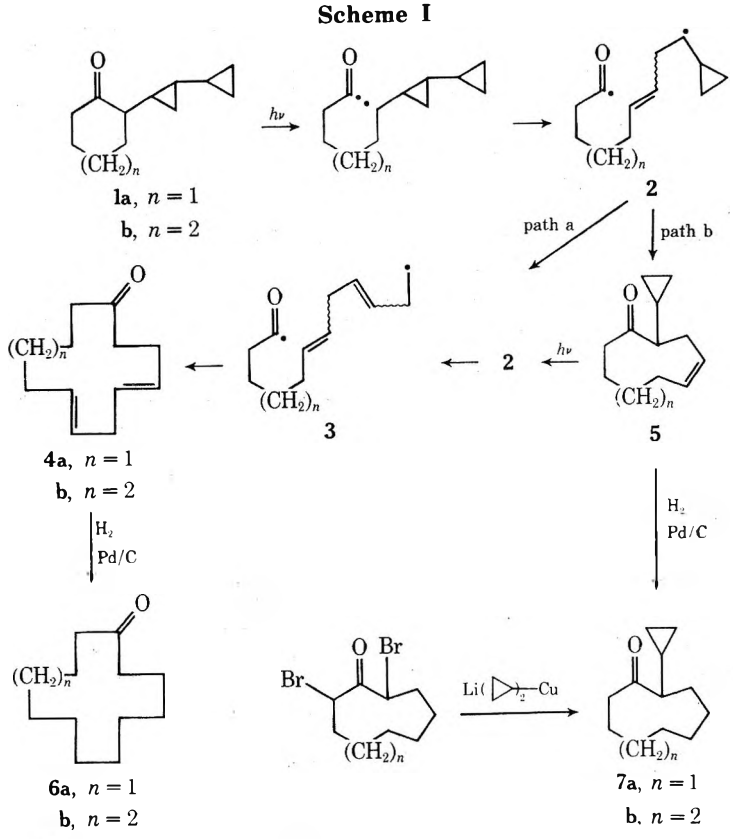
Irradiation of a dilute solution of **1a** [$\lambda_{max}^{isooctane}$ 293 nm (ϵ 34)] through Pyrex until approximately 80% of **1a** had disappeared gave a mixture which on vpc analysis was found to contain at least five products. Because of the large number of potential cis and trans double bond isomers of **4** and **5** no attempt was made to resolve the mixture. The crude photoproduct was distilled and reduced by catalytic hydrogenation over palladium on charcoal to give in 78% overall yield a mixture which contained 19% of the starting ketone **1a**, 61% cyclododecanone **6a** and 20% 2-cyclopropylcyclononanone **7a**.

A similar irradiation of 1b [$\lambda_{max}^{isooctane}$ 294 nm (ϵ 50)] to 75% disappearance of the starting material followed by hydrogenation of the distilled crude photoproduct gave in 86% overall yield a mixture of starting ketone **1b** (25%), cyclo-

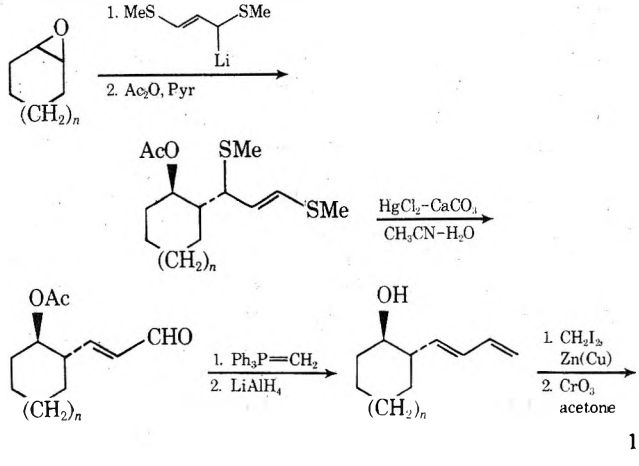
Table I
Product Composition in Photolysis of 1a

	% in Reduced Photomixture	
Time, hr	7a	6a
1	3.5	8
2	9.6	17
3	12	23

Scheme I



Scheme II



tridecanone **6b** (51%), and 2-cyclopropylcyclodecanone **7b** (24%).[9]

In an effort to determine qualitatively whether the six atom ring expanded products 4 arose by way of a one photon process (path a, Scheme I) or by two consecutive three atom ring expansions (path b) the photolysis of **1a** was stopped at low conversion and the composition of the reduced photoproduct was determined (Table I). The results of these experiments indicate that the six atom ring expanded product is a primary photoproduct because little of it would be expected to be formed early in the reaction by a two photon process as the starting ketone would be absorbing most of the light. Through the early part of the reaction the six atom and three atom ring expanded products are formed in an approximately 2:1 ratio. Since in the final product the composition is ~3:1 it appears that later in the reaction some of **5a** is being converted to **4a**.

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Received November 4, 1974

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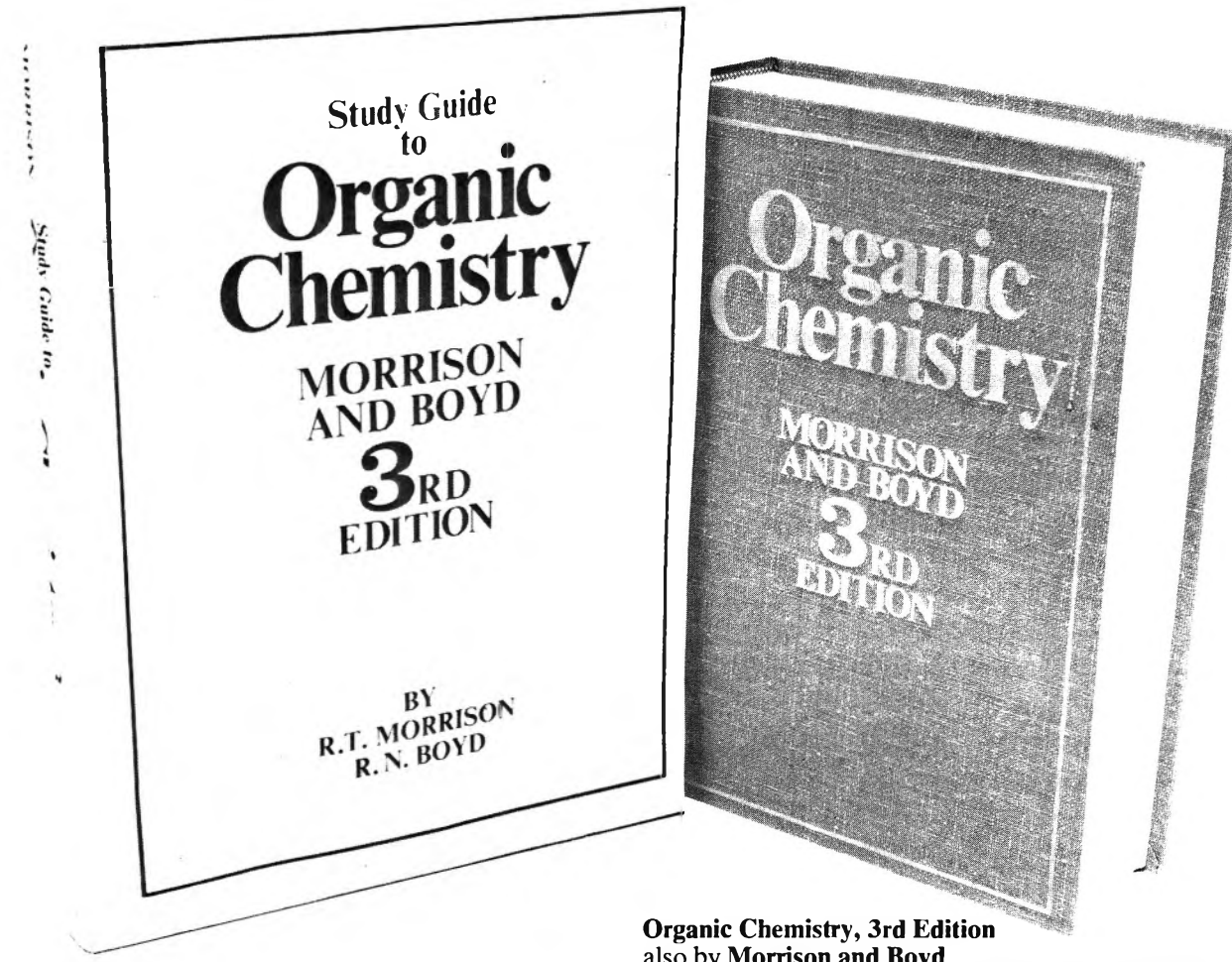

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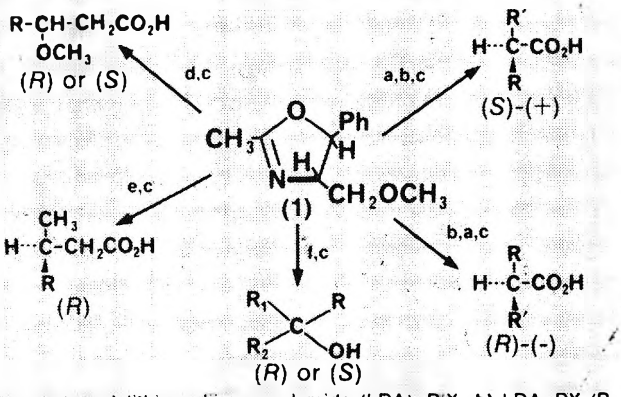
Meyers' Reagents

For asymmetric induction and two-carbon chain elongation

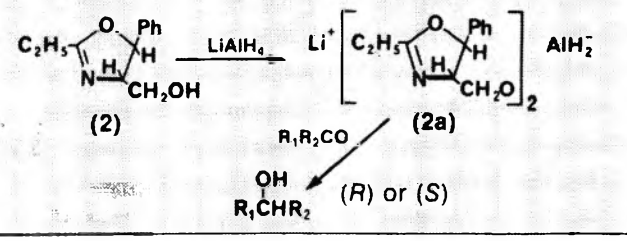


Reagents: **a)** lithium diisopropylamide (LDA), R'X **b)** LDA, RX (R precedes R', Cahn-Ingold-Prelog sequencing) **c)** H_3O^+ **d)** BuLi, RCHO, CH_3I/HMPA **e)** LDA, CH_3CHRI **f)** RMgBr, $R_1R_2C{=}O$

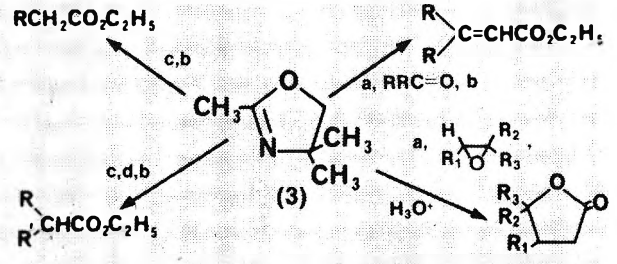
Very recently Meyers and Knaus[1] reported a versatile synthesis of *R* and *S* dialkylacetic acids from **(4*S*,5*S*)-(-)-4-methoxymethyl-2-methyl-5-phenyl-2-oxazoline (1)** *via* asymmetric induction. Thus, lithium diisopropylamide (LDA) at -78° converts the oxazoline **1** to its lithio salt. Alkylation followed by another treatment with LDA and a second alkylating agent gives, upon acid hydrolysis, the chiral acid of high optical purity (50-70%). *The order of alkyl introduction controls the stereochemistry of the final product.* When an alkyl group of lower priority (Cahn-Ingold-Prelog sequencing) is introduced, followed by a second alkyl group of higher priority, the *S* enantiomer is obtained; reversal of this order gives the *R* enantiomer.

Optically active 3-hydroxy- or 3-methoxyalkanoic acids, secondary and tertiary alcohols, and 3-methylalkanoic acids[2] also can be prepared conveniently from oxazoline **1.**

The analog, **(4*S*,5*S*)-(-)-2-ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline (2)** reacts with $LiAlH_4$ to give a chiral reducing agent **(2a)** which converts ketones to chiral secondary alcohols.[3]

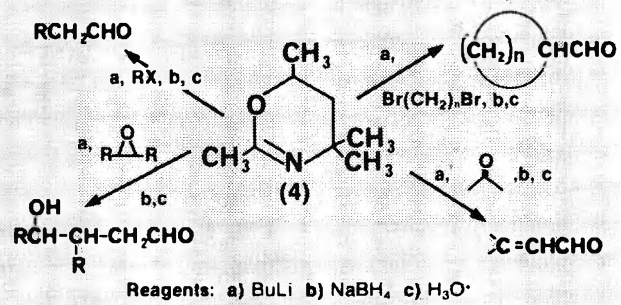


The achiral oxazoline, **2,4,4-trimethyl-2-oxazoline (3),** provides a convenient synthesis of substituted acetic acid esters, α,β-unsaturated esters and γ-butyrolactones.[4]



Reagents: **a)** BuLi **b)** H^+, C_2H_5OH **c)** BuLi, RX **d)** BuLi, R'X

5,6-Dihydro-2,4,4,6-tetramethyl-4*H*-1,3-oxazine (4) is an excellent precursor to aldehydes.[5]



Reagents: **a)** BuLi **b)** $NaBH_4$ **c)** H_3O^+

References:

1) A.I. Meyers and G. Knaus, *J. Amer. Chem. Soc.*, **96**, 6508 (1974).
2) A.I. Meyers *et al.*, *Tetrahedron Lett.*, 1333, 1341 (1974); *J. Org. Chem.*, **39**, 1603 (1974).
3) A.I. Meyers and P.M. Kendall, *Tetrahedron Lett.*, 1337 (1974).
4) A.I. Meyers *et al.*, *J. Org. Chem.*, **39**, 2778, 2783 (1974).
5) A.I. Meyers *et al.*, *ibid.*, **38**, 36 (1973).

18,765-8 **(4*S*,5*S*)-(-)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline.....5g $13.50; 25g $45.00**

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